Delaware Medical Journal

ESTABLISHED 1776 — INCORPORATED 1789

Official Publication of the Medical Society of Delaware

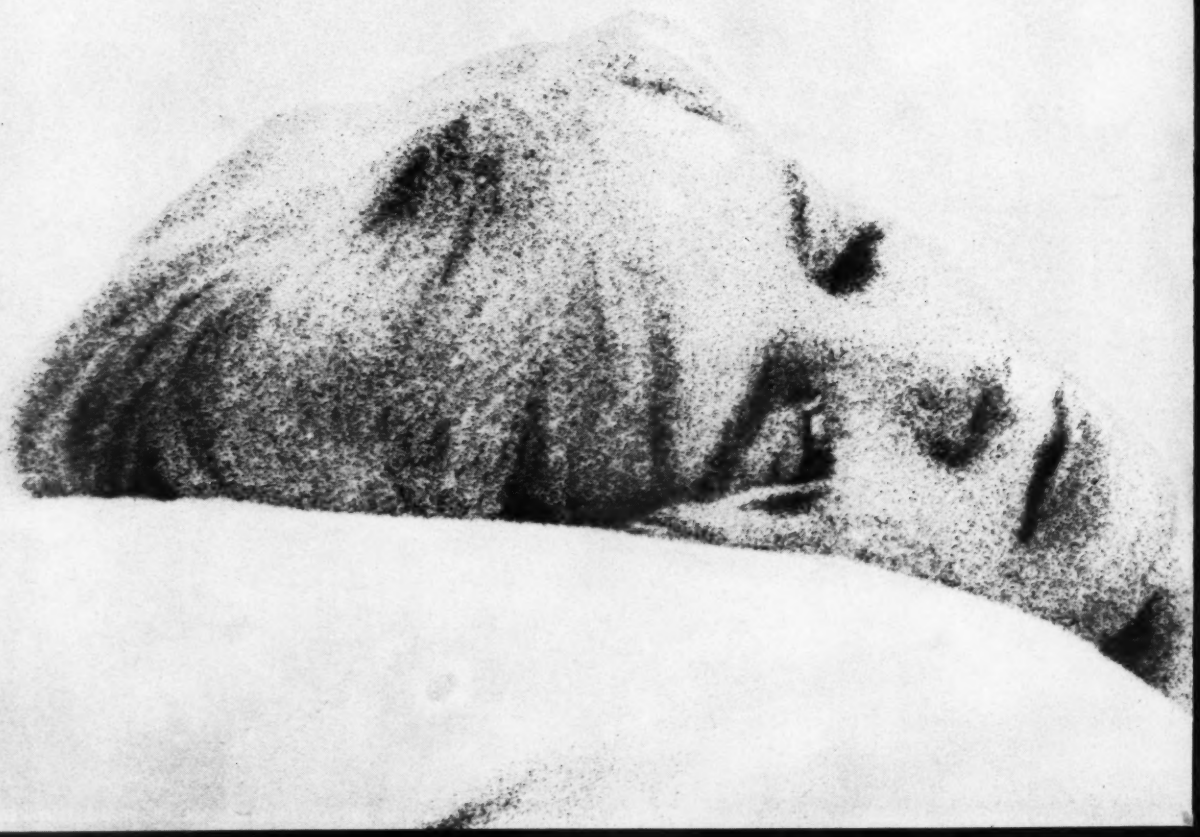
APRIL, 1961 . . .

SYMPOSIUM ON STEROIDS

because
vitamin deficiencies
tend to be multiple...
give your postoperative
patient the protection of

MYADEC®

high-potency vitamin formula with minerals



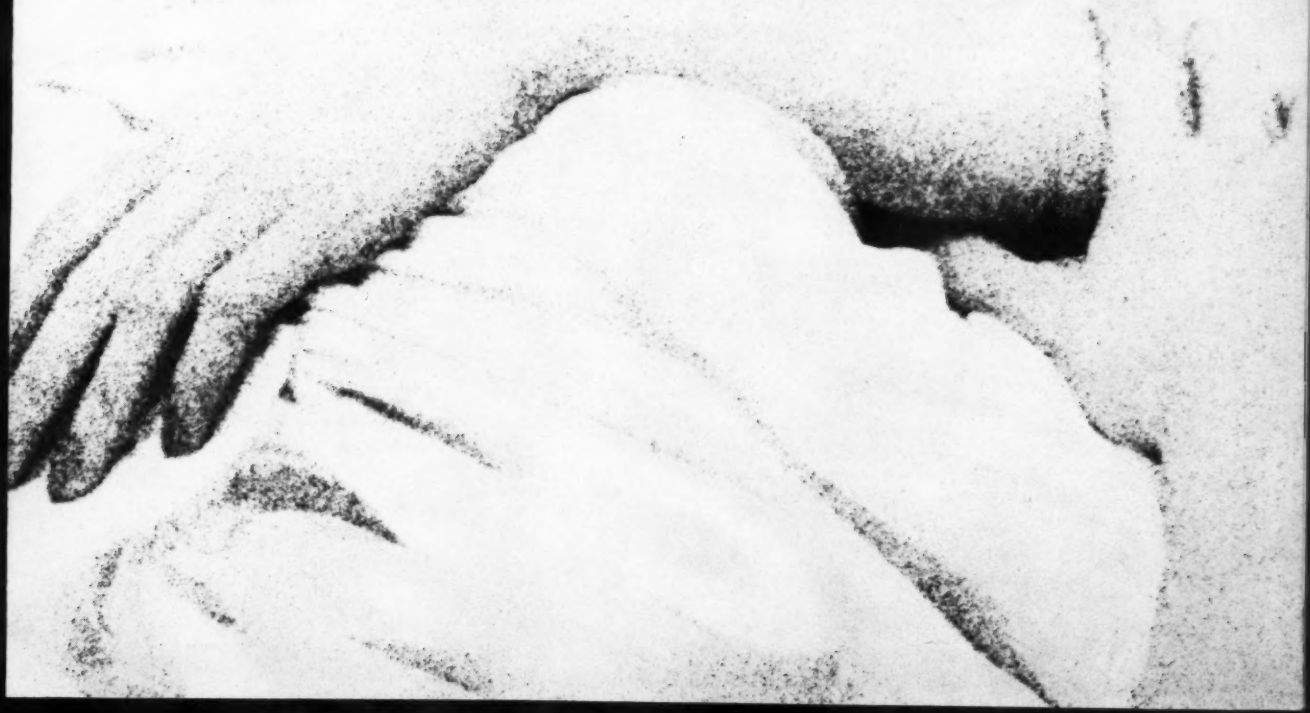
It is generally agreed that after surgery, or at other times of physiologic stress, vitamin reserves may be depleted. MYADEC helps to correct such deficiencies. Just one capsule daily supplies therapeutic potencies of 9 vitamins, *plus* various minerals normally found in body tissues. MYADEC is also valuable for the *prevention* of vitamin deficiencies in those patients whose customary diets are lacking in important food factors.

Each MYADEC capsule contains:

Vitamins: Vitamin B_{12} crystalline—5 mcg.; Vitamin B_2 (G) (riboflavin)—10 mg.; Vitamin B_6 (pyridoxine hydrochloride)—2 mg.; Vitamin B_1 mononitrate—10 mg.; Nicotinamide (niacinamide)—100 mg.; Vitamin C (ascorbic acid)—150 mg.; Vitamin A—(7.5 mg.) 25,000 units; Vitamin D—(25 mcg.) 1,000 units; Vitamin E (*d*-alpha-tocopheryl acetate concentrate)—5 I.U. ***Minerals*** (as inorganic salts): Iodine—0.15 mg.; Manganese—1 mg.; Cobalt—0.1 mg.; Potassium—5 mg.; Molybdenum—0.2 mg.; Iron—15 mg.; Copper—1 mg.; Zinc—1.5 mg.; Magnesium—6 mg.; Calcium—105 mg.; Phosphorus—80 mg. Bottles of 30, 100, and 250. 55261

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan



FOUNDED 1776
MEDICAL SOCIETY OF DELAWARE
INCORPORATED 1789

Delaware Medical Journal

Official Publication of the Medical Society of Delaware

EDITORIAL AND BUSINESS OFFICES
1925 LOVERING AVENUE, WILMINGTON 6, DELAWARE

VOLUME 33 **APRIL, 1961** **NUMBER 4**

Owned and published by the Medical Society of Delaware, a scientific non-profit corporation.

Issued the fifteenth of each month under the supervision of the Committee on Publication.

Articles are accepted for publication on condition that they are contributed solely to this JOURNAL. Manuscripts must be typewritten, double spaced, with wide margins, and the original copy submitted. Photographs and drawing for illustrations must be carefully marked and show clearly what is intended.

Footnotes and bibliographies should conform to the style of the Cumulative Index Medicus, published by the National Library of Medicine and the American Medical Association.

Changes in manuscript after an article has been set in type will be charged to the author. THE JOURNAL pays only part of the cost of tables and illustrations. Unused manuscripts will not be returned unless return postage is forwarded. Reprints may be obtained at cost, provided request is made of the printers before publication.

The right is reserved to reject material submitted for publication. THE JOURNAL is not responsible for views expressed in any article signed by the author.

All advertisements are received subject to the approval of the Committee on Publication of the Medical Society of Delaware. Advertising forms close the 15th of the preceding month.

Matter appearing in THE JOURNAL is covered by copyright. As a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given.

Subscription price: $5.00 per annum, in advance. Single copies, 75 cents. Foreign countries $5.00 per annum.

CONTENTS

Entered as second-class matter June 28, 1929, at the Post Office at Wilmington, Delaware, under the Act of March 3, 1879.
Issued monthly.

Re: *New* Nonsteroid Chemotherapy of RHEUMATOID ARTHRITIS

Dear Doctor:

The "ideal" drug for rheumatoid arthritis would be "...one that is effective in the majority of those afflicted, and of such low toxicity that it can be given, in an effective dosage, for as many years as may be necessary to control the disease process in any given patient."[1]

The two drugs that currently come closest to the definition of "ideal" are aspirin and Plaquenil®. The outstanding safety of aspirin and its effectiveness in the treatment of persons with rheumatoid arthritis have been firmly established for decades. Recent clinical studies, extending over periods of from one to five years, have demonstrated that Plaquenil inhibits rheumatoid disease in the majority of patients[1] and that it is "...the least toxic of its class..."[2]

PLANOLAR* is a combination of Plaquenil and aspirin; each tablet contains 60 mg. of Plaquenil sulfate and 300 mg. (5 grains) of aspirin. An average initial dosage of 2 PLANOLAR tablets two or three times daily produces prompt relief of pain and discomfort in the majority of patients while initiating effective long-term therapy of the rheumatoid arthritic process.

Our PLANOLAR brochure contains a complete report of clinical experience and side effects as well as more detailed information on dosage. May we send you a copy?

Sincerely yours,
WINTHROP LABORATORIES

1. Bagnall, A. W.: Antimalarial compounds in rheumatoid disease, *Canad. M.A.J.* 82:1167, June 4, 1960.
2. Cornbleet, Theodore: Discoid lupus erythematosus treated with Plaquenil, *A.M.A. Arch. Dermat.* 73:572, June, 1956.

*Planolar, trademark

Plaquenil (brand of hydroxychloroquine), trademark reg. U.S. Pat. Off.

(1022M)

New from Saunders

Nagan—Medical Almanac, 1961-62

Hundreds of facts and figures on the entire framework and operation of the medical world

Just Ready! Now under one cover you'll find a tremendous range of up-to-date data never before gathered into a single source. You can quickly check on such diverse information as: *Nobel prize winners in medicine—frequency rate of various injuries in industry—admission requirements of medical schools—number of M.D.s in major countries.* Hundreds of lists, charts, graphs and directories set forth information in quickly assimilable form. Where recentness of data is vital, you'll find statistics carried right up to 1960. Where a long record of experience is valuable, you'll find accurate figures in some cases going back to the late Seventeen Hundreds. Forthcoming meetings, tax deadlines, etc. are listed into the future. Anyone in medicine who writes, who lectures, who must document articles, or who holds some organizational duties can use this almanac daily.

Compiled by PETER S. NAGAN, A.B., M.A., M.S., 528 pages, 5½"x7¾", Paper Bound. About $5.50. *New—Just Ready!*

Over 500 pages of exhaustive facts and figures on a myriad of topics:

What medical records to keep and for how long—leading medical publications—summary of medical systems in major countries—average prevalence of peptic ulcer by sex and age—12 diagnoses with highest annual rate per 1000 patients—prevalence of chronic conditions among persons 45 years and older by age, sex—number of physicians specializing in industrial medicine—deaths and death rate from accidents by type—birth rate by color and by age of mother, 1800-1959.

Advertising medical products on TV—great epidemics of the past—leading foreign medical journals—schedule of 1961 conventions—officials and executive staff of the AMA—average income of doctors in U.S.—tuberculosis and death rate—narcotics regulations—license renewal by state—federal legislation affecting doctors.

Pillsbury, Shelley & Kligman—Manual of Cutaneous Medicine

A New Book!

Just Ready! This concise, practical manual contains a wealth of immediately applicable information on managing the entire range of cutaneous disease. It clearly illuminates the anatomy, physiology, pathology and pathophysiology of the skin. You'll find diagnosis, prevention and treatment of those skin diseases you meet most frequently in daily practice—from acne to tumors of the skin. The authors emphasize changes in the skin which may be representative of systemic disease. They assess the advantages of various treatment methods, and clearly point out potential hazards.

By DONALD M. PILLSBURY, M.A., D.Sc. (Hon.), M.D., F.A.C.P., Professor and Director of Department of Dermatology; WALTER B. SHELLEY, M.D., Ph.D., F.A.C.P., Professor of Dermatology; and ALBERT M. KLIGMAN, M.D., Ph.D., Professor of Dermatology. All of the University of Pennsylvania School of Medicine. About 440 pages, 6"x9¼", with 234 illustrations. About $10.00. *New—Just Ready!*

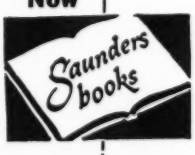
Rushmer—Cardiovascular Dynamics

New (2nd) Edition!

This valuable book provides you with the information you need to make keener diagnoses and evaluations of heart disorders. Dr. Rushmer presents a clear picture of the structure, function and control of the various components of the cardiovascular system as they exist under normal conditions—followed by the changes which occur in presence of disease. You'll find recent advances, particularly in the areas of *instrumentation and analysis of cardiac dynamics,* clearly shown. Among the topics covered are: Cardiac Output; Measurements of Pressure; Cardiovascular Sounds; Heart Size and Configuration.

By ROBERT F. RUSHMER, M.D., Professor of Physiology and Biophysics, University of Washington Medical School. 503 pages, 6½"x10", with 264 illustrations. $12.50. *Just Published—New (2nd) Edition!*

Order Now



SJG-4-61

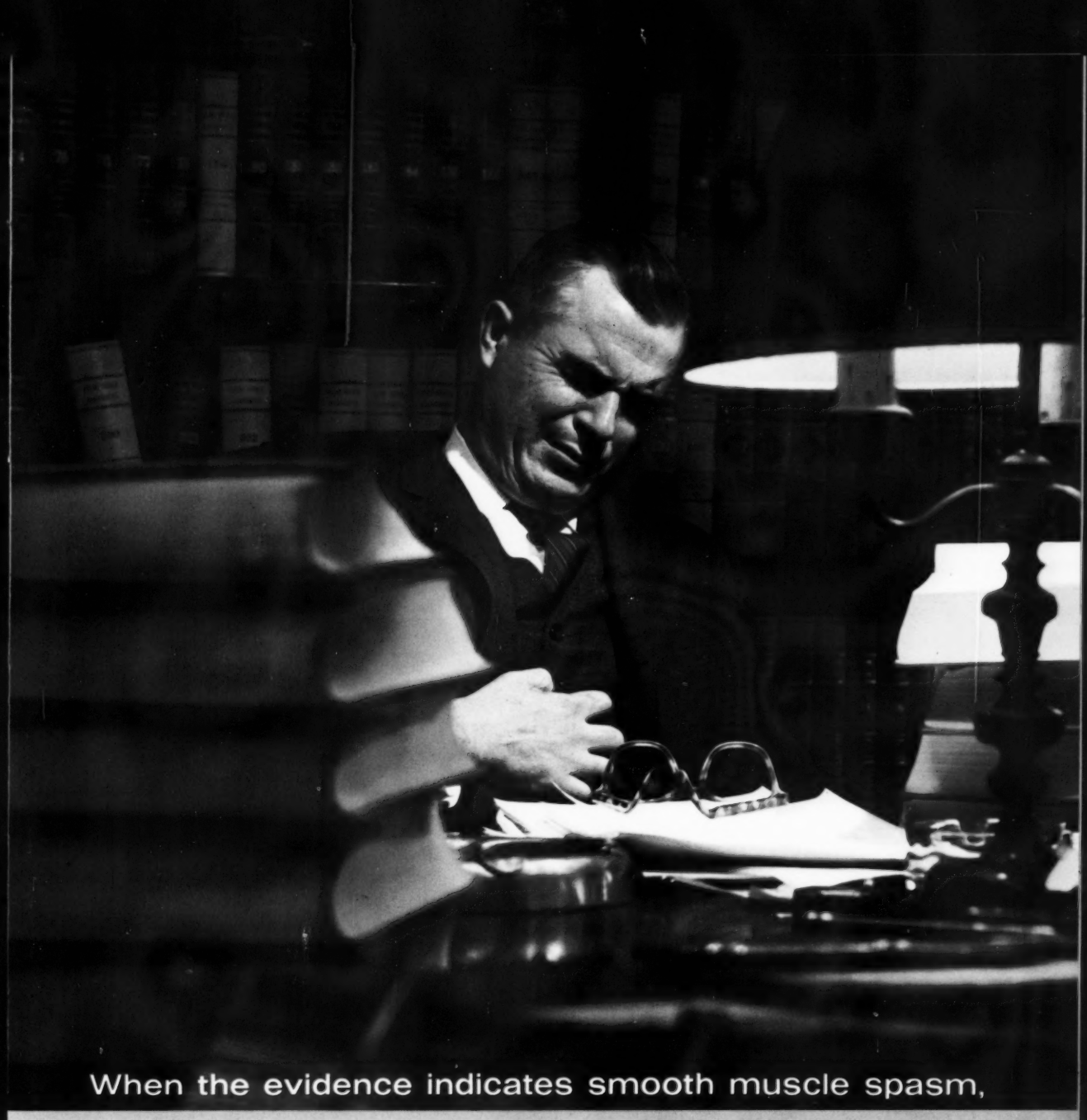
W. B. SAUNDERS COMPANY
West Washington Square, Philadelphia 5

Please send me the following books and charge my account:

- ☐ Nagan's Medical Almanac, 1961-62, about $5.50
- ☐ Pillsbury et al., Manual of Cutaneous Medicine, about $10.00
- ☐ Rushmer's Cardiovascular Dynamics, $12.50

Name_____

Address_____



When the evidence indicates smooth muscle spasm,

good judgment can render it "null and void"
by a ruling in favor of
dependable autonomic sedation

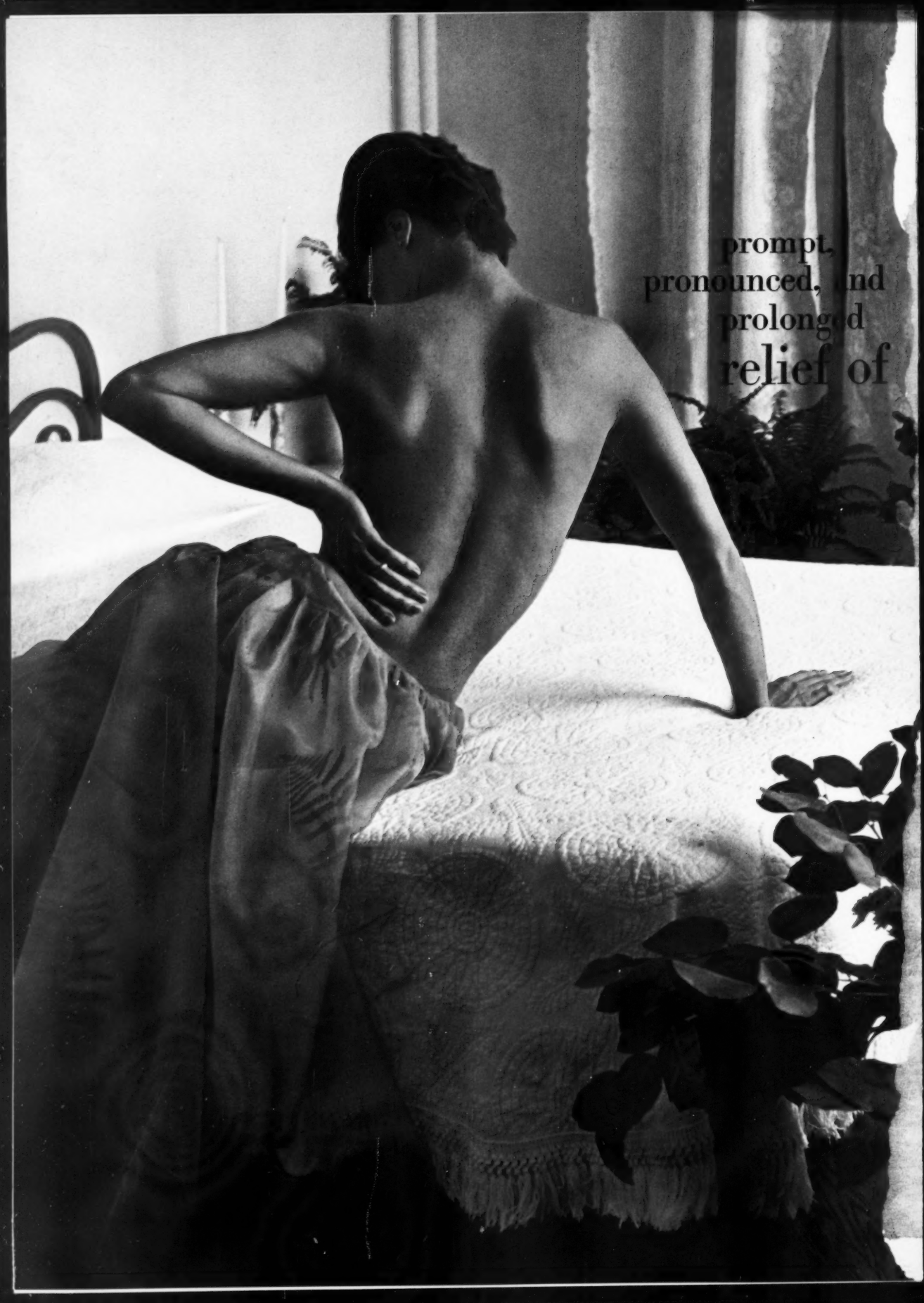
DONNATAL®

TABLETS • CAPSULES • ELIXIR • EXTENTABS

Natural belladonna alkaloids in optimal synergistic ratio, plus phenobarbital

A. H. ROBINS CO., INC., Richmond 20, Virginia

	In each Tablet, Capsule or tsp. (5 cc.) of Elixir	In each Extentab
Hyoscyamine sulfate	0.1037 mg.	0.3111 mg.
Atropine sulfate	0.0194 mg.	0.0582 mg.
Hyoscine hydrobromide	0.0065 mg.	0.0195 mg.
Phenobarbital	(¼ gr.) 16.2 mg.	(¾ gr.) 48.6 mg.


prompt,
pronounced, and
prolonged
relief of

painful skeletal muscle spasm

ROBAXIN®

Robins

INJECTABLE AND TABLETS Methocarbamol Robins U.S. Pat. No. 2770649

Relaxation – obtained *within minutes* with ROBAXIN Injectable.
– maintained *without drowsiness* with ROBAXIN Tablets.

Nine published studies show:

Beneficial results in 90% of cases of skeletal muscle spasm with ROBAXIN.

Clinical responses to ROBAXIN therapy, as reported by investigators:

"*marked*" in 26 out of 33 patients, moderate in 6...[1] "*pronounced*" in 37 out of 58 patients, moderate in 20...[2] "*good*" in 25 out of 38 patients, moderate in 6...[5] "*excellent*" in 14 out of 17 patients, moderate in 2...[6] "*significant*" in 27 out of 30 patients...[7] "*gratifying*" in 55 out of 60 patients...[8] "*effective*" in 32 out of 32 patients...[9] "*marked*" in 27 out of 46 patients, moderate in 6...[4] "*good*" in 57 out of 60 patients, moderate in 3.[10]

ROBAXIN exhibits "great freedom from undesired side reactions,"[3] does not produce "concomitant euphoria or partial anesthesia,"[10] and permits patients to retain concentration and awareness.[8]

For immediate relaxation of acute skeletal muscle spasm:

Robaxin® Injectable – **each ampul containing 1.0 Gm. of methocarbamol in 10 cc. of sterile solution.**

For initiating therapy or maintaining relaxation induced by* ROBAXIN *Injectable:

Robaxin® Tablets – **0.5 Gm. (white, scored) in bottles of 50 and 500.**

Also available: *When pain and spasm require concurrent analgesic and relaxant action:*

Robaxisal® Tablets – **Robaxin with Aspirin**

–and for skeletal muscle relaxation with more comprehensive analgesia:

Robaxisal®– PH – **Robaxin with Phenaphen®**

Literature available to physicians on request.

REFERENCES: 1. Carpenter, E. B.: Southern M.J. 51:627, 1958. **2.** Forsyth, H. F., J.A.M.A. 167:163, 1958. **3.** Hudgins, A. P.: Clin. Med. 6:2321, 1959. **4.** Grisolia, A., and Thomson, J. E. M.: Clin. Orthopaedics 13:299, 1959. **5.** Lewis, W. B.: California Med. 90:26, 1959. **6.** O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. **7.** Park, H. W.: J.A.M.A. 167:168, 1958. **8.** Plumb, C. S.: Journal-Lancet 78:531, 1958. **9.** Poppen, J. L., and Flanagan, M. E.: J.A.M.A. 171:298, 1959. **10.** Schaubel, H. J.: Orthopedics 1:274, 1959.

A. H. ROBINS CO., INC., Richmond 20, Virginia

Making today's medicines with integrity . . . seeking tomorrow's with persistence

"nutrition...present as a modifying or complicating factor in nearly every illness or disease state"[1]

1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958

cardiac diseases "Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2] 2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

arthritis "It is our practice to prescribe a multiple vitamin preparation to patients with rheumatoid arthritis simply to insure nutritional adequacy . . ."[3]
3. Fernandez-Herlihy, L.: Lahey Clinic Bull. 11:12 (July-Sept.) 1958.

digestive diseases Symptoms attributable to B-vitamin deficiency are commonly observed in patients on peptic ulcer diets.[4] Daily administration of therapeutic vitamins to patients with hepatitis and cirrhosis is recommended by the National Research Council.[5] 4. Sebrell, W. H.: Am. J. Med. 25:673 (Nov.) 1958. 5. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition. National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 57.

degenerative diseases "Studies by Wexberg, Jolliffe and others have indicated that many of the symptoms attributed in the past to senility or to cerebral arteriosclerosis seem to respond with remarkable speed to the administration of vitamins, particularly niacin and ascorbic acid. These facts indicate that the vitamin reserve of aging persons is lowered, even to the danger point, more than is the case in the average American adult."[6] 6. Overholser, W., and Fong, T. C. C. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition. J. B. Lippincott, Philadelphia, 1954, p. 264.

infectious diseases Infections cause a lowering of ascorbic acid levels in the plasma; and the absorption of this vitamin is reduced in diarrheal states.[7] 7. Goldsmith, G. A.: Conference on Vitamin C. The New York Academy of Sciences, New York City, Oct. 7 and 8, 1960. Reported in: Medical Science 8:772 (Dec.10) 1960.

diabetes Diabetics, like all patients on restricted diets, require an extra source of vitamins.[8] "Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet. . . . There is some evidence of interference with normal riboflavin utilization during catabolic episodes."[9]
8. Duncan, G. G.: Diseases of Metabolism. 4th edition. W. B. Saunders, Philadelphia, 1959, p. 812. 9. Pollack, H.: Am. J. Med. 25:708 (Nov.) 1958.

ANNOUNCING—
SPECIFICALLY FOR
INFECTIONS DUE TO
"RESISTANT" STAPHYLOCOCCI

AN ENTIRELY NEW SYNTHETIC
"STAPH-CIDAL" PENICILLIN

Staphcillin™

sodium dimethoxyphenyl penicillin
FOR INJECTION

UNIQUE—BECAUSE IT
RETAINS ANTIBACTERIAL
ACTIVITY IN THE PRESENCE OF
STAPHYLOCOCCAL PENICILLINASES
WHICH INACTIVATE
OTHER PENICILLINS

Bristol™

CUT HERE FOR FILING

NEW SYNTHETIC PENICILLIN FOR "RESISTANT" STAPH

OFFICIAL PACKAGE CIRCULAR
November, 1960

STAPHCILLIN™

(sodium dimethoxyphenyl penicillin)

For Injection

DESCRIPTION

STAPHCILLIN is a unique new synthetic parenteral penicillin produced by Bristol Laboratories for the specific treatment of staphylococcal infections due to resistant organisms. Its uniqueness resides in its property of resisting inactivation by staphylococcal penicillinase. It is active against strains of staphylococci which are resistant to other penicillins.

Each dry filled vial contains: 1 Gm. STAPHCILLIN (sodium dimethoxyphenyl penicillin), equivalent to 900 mg. dimethoxyph nyl penicillin activity.

INDICATIONS

STAPHCILLIN is recommended as specific therapy only in infections due to strains of staphylococci resistant to other penicillins, e.g.:

Skin and soft tissue infections: cellulitis, wound infections, carbuncles, pyoderma, furunculosis, lymphangitis and ymphadenitis.

Respiratory infections: staphylococcal lobar or bronchopneumonia, and lung abscesses combined with indicated surgical treatment.

Other infections: staphylococcal septicemia, bacteremia, acute or subacute endocarditis, acute osteomyelitis and enterocolitis.

Infections due to penicillin-sensitive staphylococci, streptococci, pneumococci and gonococci should be treated with Syncillin® or parenteral penicillin G rather than STAPHCILLIN. Treponemal infections should be treated with parenteral penicillin G.

DOSAGE AND ADMINISTRATION

STAPHCILLIN is well tolerated when given by deep intragluteal or intravenous injection.

As is the case with other antibiotics, the duration of therapy should be determined by the clinical and bacteriological response of the patient. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic and cultures are negative. The usual duration has been 5-7 days.

Intramuscular route: The usual adult dose is 1 Gm. every 4 or 6 hours. Infants' and children's dosage is 25 mg. per Kg. (approximately 12 mg. per pound) every 6 hours.

Intravenous route: 1 Gm. every 6 hours using 50 ml. of sterile saline solution at the rate of 10 ml. per minute.

**Warning:* Solutions of STAPHCILLIN and kanamycin should not be mixed, as they rapidly inactivate each other. Data on the results of mixing STAPHCILLIN with other antibiotics are being accumulated.

DIRECTIONS FOR RECONSTITUTION

Add 1.5 ml. sterile distilled water or normal saline to a 1 Gm. vial and shake vigorously. Withdraw the clear, reconstituted solution (2.0 ml.) into a syringe and inject. The reconstituted solution contains 500 mg. of STAPHCILLIN per ml. Reconstituted solutions are stable for 24 hours under refrigeration.

For intravenous use, dilute the reconstituted dose in 50 ml. of sterile saline and inject at the rate of 10 ml. per minute.

*This statement supersedes that in the Official Package Circulars dated September and/or October, 1960.

(continued)

CUT HERE FOR FILING

OFFICIAL PACKAGE CIRCULAR
(continued)

MICROBIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

In vitro studies show that STAPHCILLIN is a bactericidal penicillin with activity against staphylococci resistant to penicillin G. Strains of staphylococci so far tested have been sensitive to STAPHCILLIN *in vitro* at concentrations of 1-6 mcg. per ml. These levels are readily attained in the blood and tissues by administration of STAPHCILLIN at the recommended dosage. This unique attribute is probably due to the fact that STAPHCILLIN is stable in the presence of staphylococcal penicillinase. STAPHCILLIN also resists degradation by *B. cereus* penicillinase. The antimicrobial spectrum of STAPHCILLIN with regard to other microorganisms is qualitatively similar to that of penicillin G; but considerably higher concentrations of STAPHCILLIN are required for bactericidal activity than is the case with penicillin G.

STAPHCILLIN is rapidly absorbed after intramuscular injection. Peak blood levels (6-10 mcg./ml. on the average after a 1.0 Gm. dose) are attained within 1 hour; and then progressively decline to less than 1 mcg. over a 4 to 6 hour period. It is poorly absorbed from the gastrointestinal tract. STAPHCILLIN is rapidly excreted by the kidney.

As shown by animal studies, STAPHCILLIN is readily distributed in body tissues after intramuscular injection. Of the tissues studied, highest concentrations are reached in the kidney, liver, heart and lung in that order; the spleen and muscles show lower concentrations of the antibiotic. STAPHCILLIN diffuses into human pleural and prostatic fluids, but its diffusion into the spinal fluid has not yet been completely studied. However, one patient with meningitis showed a significant concentration in his spinal fluid while on STAPHCILLIN therapy.

Toxicity studies with STAPHCILLIN and penicillin G in animals show that they have approximately the same low order of toxicity.

Certain staphylococci can be made resistant to STAPHCILLIN in the laboratory, but this resistance is not related to their penicillinase production. During the clinical trials, no STAPHCILLIN-resistant strains of staphylococci were observed or developed; the possibility of the emergence of such strains in the clinical setting awaits further observation.

PRECAUTIONS

During the clinical trials, several mild skin reactions, e.g., itching, papular eruption and erythema were observed both during and after discontinuance of STAPHCILLIN therapy. Patients with histories of hay fever, asthma, urticaria and previous sensitivity to penicillin are more likely to react adversely to the penicillins. It is important that the possibility of penicillin anaphylaxis be kept in mind. Epinephrine and the usual adjuvants (antihistamines, corticosteroids) should be available for emergency treatment. Because of the resistance of STAPHCILLIN to destruction by penicillinase, parenteral *B. cereus* penicillinase may not be effective for the treatment of allergic reactions. Information with regard to cross-allergenicity between penicillin G, penicillin V, phenethicillin (Syncillin) and STAPHCILLIN is not available at present. If superinfection due to Gram-negative organisms or fungi occurs during STAPHCILLIN therapy, appropriate measures should be taken.

SUPPLY

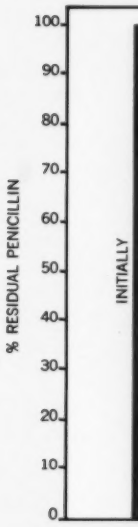
List 79502 — 1.0 Gm. dry filled vial.

BRISTOL LABORATORIES · SYRACUSE, NEW YORK
Division of Bristol-Myers Company

CUT HERE FOR FILING

UNIQUE SYNTHETIC "STAPH-CIDAL" PENICILLIN

CUT HERE FOR FILING



Specific

St

The failure of st
the penicillin-des

Unlike other pen

1 STAPHCILLIN
ence of staphyloc

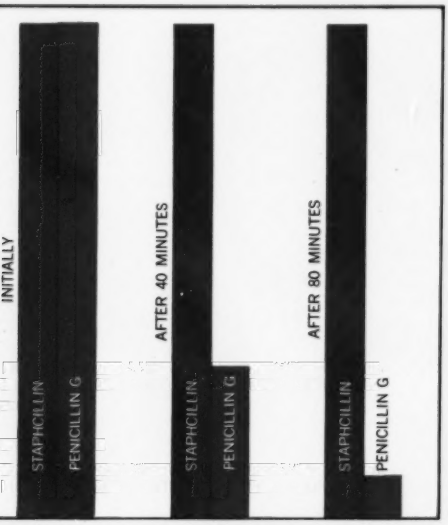
2 The clinical
a wide variety of
and life-threateni

Like other penici

STAPHCILLIN
pain or irritation
penicillin G. *In*

PROFESSIONAL
plete information
additional inform
Bristol Laboratori
PLaza 7-7061, or

BRISTOL



In the presence of staphylococcal penicillinase, STAPHCILLIN remained active and retained its antibacterial action. By contrast, penicillin G was rapidly destroyed in the same period of time. *(After Gourevitch et al., to be published)*

cally for "resistant" staph...

taphcillin™

sodium dimethoxyphenyl penicillin
FOR INJECTION

staphylococcal infections to respond to penicillin therapy is attributed to destroying enzyme, penicillinase, produced by the invading staphylococcus.

enicillins:

IN is effective because it retains its antibacterial activity despite the pres- ococcal penicillinase.

al effectiveness of STAPHCILLIN has been confirmed by dramatic results in of infections due to "resistant" staphylococci, many of which were serious ening.

icillins:

IN has no significant systemic toxicity. It is well tolerated locally, and ion at the injection site is comparable to that following the injection of *n occasional cases, typical penicillin reactions may be experienced.*

AL INFORMATION SERVICE – The attached Official Package Circular provides com- on on the indications, dosage, and precautions for the use of STAPHCILLIN. If you desire rmation concerning clinical experiences with STAPHCILLIN, the Medical Department of ories is at your service. You may direct your inquiries via collect telephone call to New York, or by mail to Medical Department, Bristol Laboratories, 630 Fifth Ave., N. Y. 20, N. Y.

L LABORATORIES • SYRACUSE, NEW YORK
Division of Bristol-Myers Company

Lifts depression...as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety...rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety – both at the same time.

Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function – frequently reported with other antidepressant drugs.

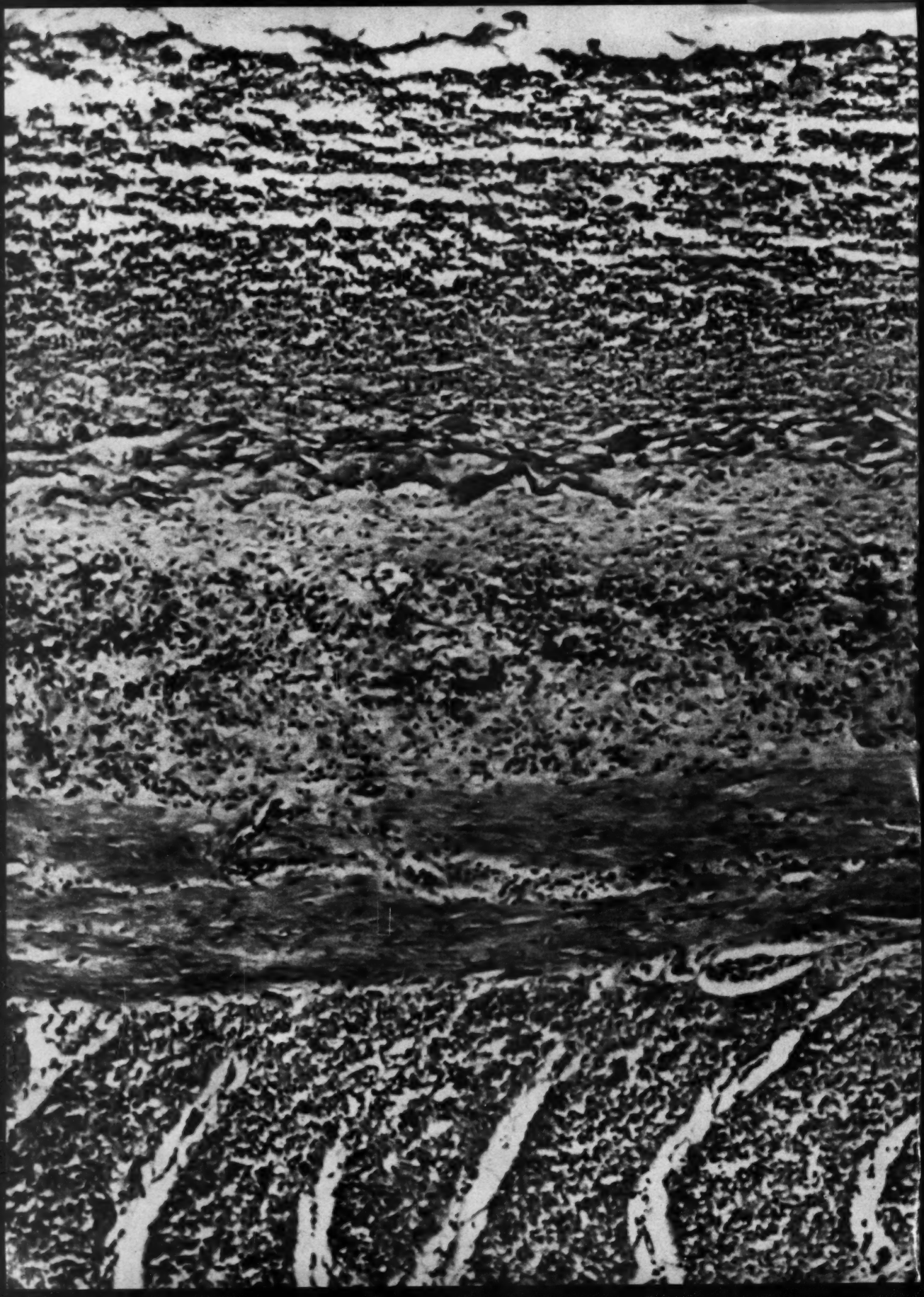
Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

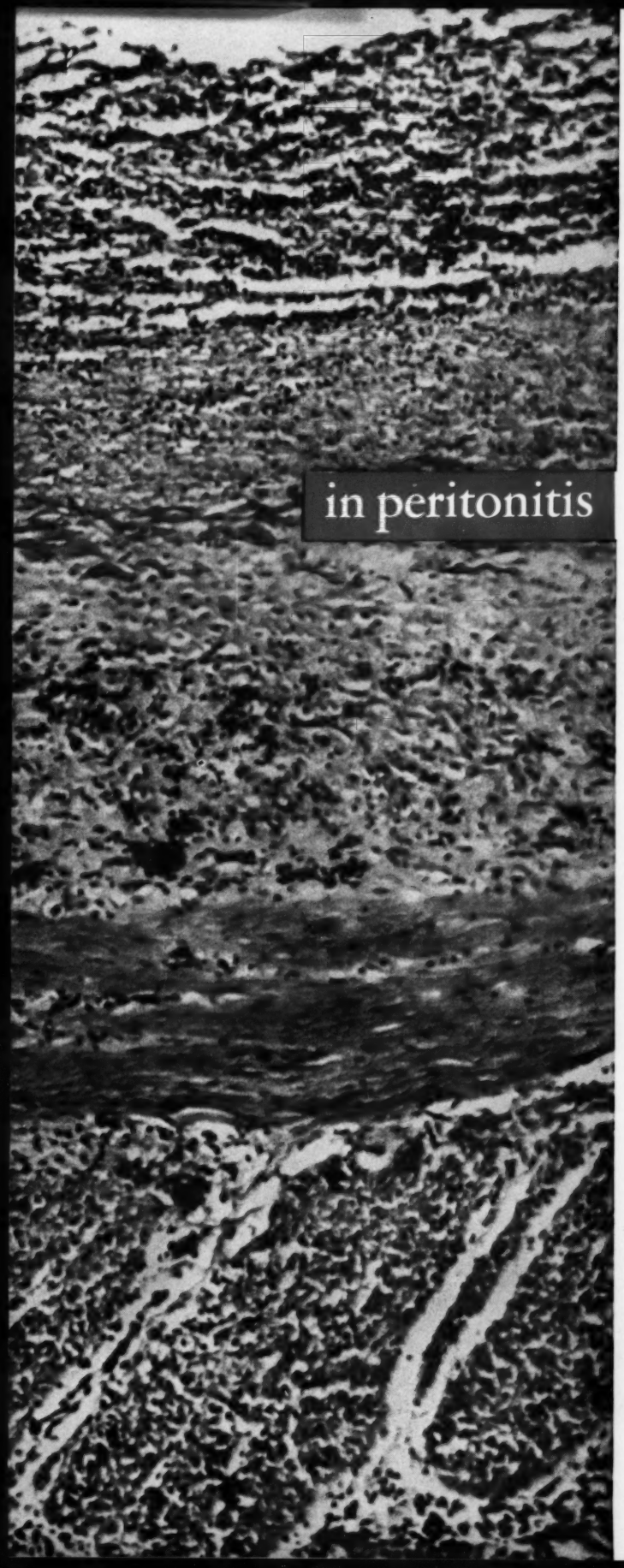
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate. **Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲®

WALLACE LABORATORIES/ *Cranbury, N. J.*

CD-2839





Therapeutic confidence

Panalba is effective against more than 30 commonly encountered pathogens including ubiquitous staphylococci. Right from the start, prescribing it gives you a high degree of assurance of obtaining the desired anti-infective action in this as in a wide variety of bacterial diseases.

Supplied: Capsules, each containing Panmycin* Phosphate (tetracycline phosphate complex), equivalent to 250 mg. tetracycline hydrochloride, and 125 mg. Albamycin,* as novobiocin sodium, in bottles of 16 and 100.

Adult dosage: 2 capsules four times a day.

Side effects: Panmycin Phosphate has a very low order of toxicity comparable to that of the other tetracyclines and is well tolerated clinically. Side reactions to therapeutic use in patients are infrequent and consist principally of mild nausea and abdominal cramps.

Albamycin also has a relatively low order of toxicity. In a certain few patients, a yellow pigment has been found in the plasma. This pigment, apparently a metabolic by-product of the drug, is not necessarily associated with abnormal liver function tests.

Urticaria and maculopapular dermatitis, a few cases of leukopenia, and agranulocytosis have been reported in patients treated with Albamycin. All of these side effects rapidly disappeared upon discontinuance of the drug.

Caution: Since the use of any antibiotic may result in overgrowth of nonsusceptible organisms, constant observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken.

As with any serious infection, therapy of peritonitis with Panalba or other antibacterial agents is adjunctive to surgical procedures and supportive therapy.

Inflammatory process of the peritoneum

The Upjohn Company
Kalamazoo, Michigan

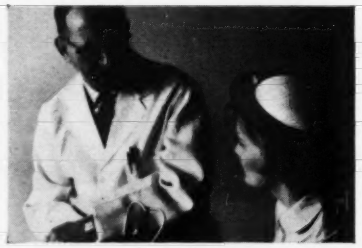
Upjohn

75th year

*Trademark, Reg. U. S. Pat. Off.

Panalba*

your broad-spectrum antibiotic of *first* resort



SUCCESSFUL FAMILY PLANNING...BASED ON YOUR COUNSEL AND **LANESTA® GEL**

Every young couple about to be married needs advice of all sorts, and they'll get it, too — from everybody — some good, some bad. But some of the most valuable counsel they can get — help in planning their own family — comes best from you. Their family happiness for many years can depend on what you suggest to them, including your recommendation for the use of Lanesta Gel.

Lanesta Gel, with or without a diaphragm, is a most effective means of conception control. Lanesta Gel offers faster spermicidal action because it rapidly diffuses into the seminal clot. In fact, Gamble ("Spermicidal Times of Commercial Contraceptive Materials — 1959"*) *found the mean diffusion spermicidal time of Lanesta Gel to be three to seven times faster than the mean diffusion times of ten leading commercially available contraceptive creams, gels, or jellies.*

Lanesta Gel has complete esthetic acceptance and is well tolerated. *Gamble, C. P.: Am. Pract. & Digest. Treat. *11*:852 (Oct.) 1960.

A PRODUCT OF LANTEEN® RESEARCH BREON Distributed by
Supplied by Esta Medical Laboratories, Inc., Alliance, Ohio BREON LABORATORIES INC., New York 18, N. Y.

an added measure of protection for little patients

against relapse
against "problem" pathogens

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

pediatric drops
syrup

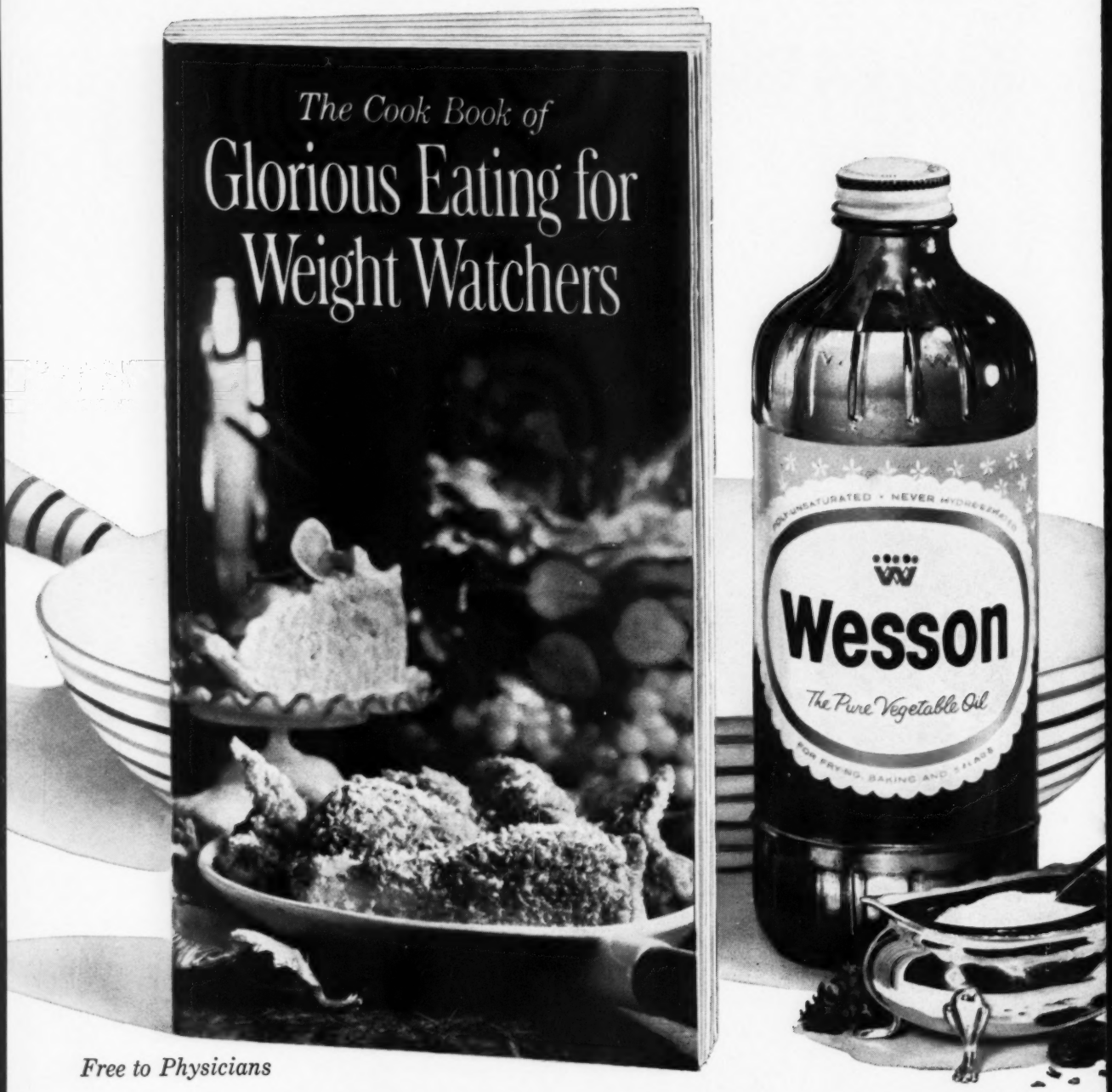
● full antibiotic activity ● lower milligram intake per dose ● up to 6 days' activity with 4 days' dosage ● uniformly high, sustained peak activity ■ **syrup** (cherry-flavored), 75 mg./5 cc. tsp., bottles of 2 and 16 fl. oz. Dosage: 3 to 6 mg./lb./day—in four divided doses. **pediatric drops,** 60 mg./cc., 3 mg./drop, 10 cc. bottles with calibrated dropper. Dosage: 1 to 2 drops/lb./day—in four divided doses.

PRECAUTIONS: As with many other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs discontinue medication. Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under observation.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York Lederle

A REALISTIC AID TO PROPER WEIGHT MAINTENANCE

At Last...New Cook Book Designed



Free to Physicians

Menus fulfill the recommended dietary allowances of the Food & Nutrition Board of the National Research Council.

to Prevent Overweight Through Better Eating Habits

Recipes and Menus with Satiety and Appetite Appeal in Mind

The Cook Book of Glorious Eating for Weight Watchers fills the long-felt need for a weight control plan that is workable for everybody in the family. Realistic regimens are built around good, natural, readily-available foods enhanced by delicious methods of preparation. In place of "fad diets" or tasteless formulas, it provides for truly appetizing meals. It teaches and encourages the development of the healthful eating habits that can prevent overweight, America's #1 Health Problem. This full-color cook book contains 100 pages—248 delicious recipes each with calorie counts. Complete menus are here at 3 calorie levels—1200, 1800, 2600. Calorie levels are related to *best* weights by sex, age, size and extent of activity.

Many diets fail because they are crash programs only temporary in effect. Other diets are unbearable because they are monotonous and tasteless.

The Wesson way is not a crash program. It offers calorie controlled menus with appetite appeal, variety and satiety in mind. They fulfill the recommended dietary allowances of the Food & Nutrition Board of the National Research Council.

All menus provide the proper amount of protein, carbohydrates, fat and the other essential nutrients. The principles of good nutrition are included to help the homemaker plan her own properly balanced, calorie controlled menus. With simple subtractions or additions to the same basic menu, each family member can be served delicious satisfying menus according to his individual needs.

Not a reducing manual. It should be explained that "The Cook Book of Glorious Eating for Weight Watchers" is a guide to the *prevention of obesity.* Its publication marks the first time that a food manufacturer like Wesson has taken so important a step to help combat this serious public health problem.

Copies for physicians. "The Cook Book of Glorious Eating for Weight Watchers" is being offered to the general public. If you would like a copy for yourself, together with forms to enable patients to obtain their own copies, please fill in coupon below.

Note: *Please do not confuse this booklet with the Cholesterol Depressant Diet Book, published by Wesson as an aid to physicians and* for professional distribution only. *The concept of the Cholesterol Depressant Diet Book stems from Wesson's value in cholesterol depressant diets. Where a vegetable (salad) oil is medically recommended for a cholesterol depressant regimen, poly-unsaturated Wesson is unsurpassed by any readily available brand.*

The Wesson People, Dept. M, 210 Baronne St., New Orleans 12, La.

Please send me my copy of "The Cook Book of Glorious Eating for Weight Watchers", plus two dozen order blanks for distribution to my patients.

_____ M.D.

ADDRESS _____

CITY, ZONE, STATE _____

Poly-unsaturated **Wesson,** *the Pure Vegetable Oil, is Never Hydrogenated*

without steroids this arthritic miner might still be spoon-fed

On METICORTEN, he has worked steadily for six years with no serious side effects

J. G.'s rheumatoid arthritis started in 1949 with severe and unremitting pain in his shoulders. Later, his wrists, elbows, feet and hands became involved with swelling and loss of function. By 1951, when he was 45, the patient was helpless and had to be fed and dressed by his wife. He was frequently hospitalized during the next three years. Hydrocortisone failed to make any change in his condition.

On April 2, 1955, the patient was placed on METICORTEN and improved promptly. Two weeks later he stated, "I feel very well now." He was able to go back to work as a mine electrician that year and had no difficulty driving a car.

For the past six years, he has been maintained on METICORTEN 5 mg. two or three times a day. There have been no side effects. The patient has not lost any work time, nor has he had to limit his activities in any way.

Case history courtesy of Joel Goldman, M.D., Johnstown, Pa. These photographs of Dr. Goldman's patient were taken on November 10, 1960.

METICORTEN,® brand of prednisone.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

S-733

APRIL, 1961
NUMBER 4
VOLUME 33

Delaware Medical Journal

SYMPOSIUM ON STEROIDS†

INTRODUCTORY REMARKS

LEWIS B. FLINN, M.D.

It has been one of the most important purposes, as laid down in the original charter of the Academy of Medicine, to stimulate, promote and carry on education, particularly in the profession and also in the community. This Seminar today is an instance of this educational activity and I am sure will prove to be a most interesting and stimulating one.

The steroids have been available to the practicing physician for perhaps ten or twelve years, and there has been much written about them. They, as you know, have been used for everything from ingrown toenails to dandruff. The subject has become almost hackneyed, and along with it a tremendous amount of confusion. Certainly at times their use is almost miraculous, at times in saving lives. Certainly their misuse causes a lot of damage. And I think it can be said without serious objection that steroids have never cured anybody of anything. Yet they are a most interesting and most varied group of medications. The various types of steroids may perhaps today be clarified. Whether one is better than another is often questionable, perhaps too frequently we depend upon the last detail man who visits the office. Nevertheless, they are a most important adjunct in the treatment of patients.

Today we have individuals who will speak to us on particular aspects of this problem, men who have had experience and training in these special areas and who will be able to tell us the important use and the pitfalls to avoid in the various fields in which they are particularly interested.

When one thinks of the dramatic effect which at times can be produced in certain eye diseases, in asthma, some cases of urticaria, perhaps assisting in a dramatic symptomatic improvement in such diseases as typhoid fever or the rickettsial diseases, to mention just a few, and perhaps lessening the damage and shortening the course in acute rheumatic carditis, a disease which fortunately seems to be on the wane in the last few years—all this is encouaging.

But when one is presented with a patient who has become addicted to these drugs from too long use in too large a dosage, and sees a patient die not from the disease but from the steroid administration, one is often confused as to when, in what dosage and how long to use one or more steroids.

Therefore, it is of particular importance to all of us to try to become better informed about this important aid in the treatment of patients, and therefore we look forward to the addresses we are about to hear and to the panel discussion which will follow, where all of us will have an opportunity to ask questions which are still perhaps left in our minds.

†Held on November 7th, 1959 at the Delaware Academy of Medicine, Wilmington, Delaware.

Dr. Flinn is a founder and first president of the Delaware Academy.

STEROIDS IN ULCERATIVE COLITIS AND IN HEPATIC DISEASE

● **While steroids offer no cure in these treatment-resistant conditions, they do give the greatest hope of all forms of present day treatment.**

HENRY J. TUMEN, M.D.

The original topic assigned to me was "*The Use of Steroids in Patients with Gastrointestinal Diseases.*" I took the liberty of shortening my discussion to ulcerative colitis and liver disease. Perhaps I should have shortened it further because both of these are extremely difficult to cover briefly and dogmatically.

As I thought about what I should say this morning, I realized how careful one must be in the selection of words, probably even more careful than a television commentator, because certainly when we talk about these diseases, ulcerative colitis and various liver diseases, the use of a term like "cure" is very, very bad. We have to state almost immediately that these drugs, ACTH and steroids, hardly can be spoken of as "curing" these conditions.

Ulcerative colitis, of course, is a disease in which it is extremely difficult to evaluate any form of therapy. Ulcerative colitis is a disease of unknown etiology, variable and unpredictable course, many complications, and completely uncertain prognosis. To try to weigh the results of therapy in a disease like this is very hard, particularly when we don't know exactly what the therapy does and how it acts.

If we look at the problem from a statistical standpoint we know that years ago, before we had steroids, back in the "Dark Ages", the results of the management of ulcerative colitis were not entirely bad. Approximately twenty percent of patients who were followed for a reasonable period of time had a complete remission of symptoms; maybe another twenty percent had mild recurrences that were not terribly incapacitating; about twenty percent continued to have disease that was of major severity; maybe another twenty percent came to surgery and were cured in the sense that their colons were removed; and possibly twenty percent would die of the disease over a period of eight or ten years of follow-up. But we did have some patients who recovered in the sense that their disease became quiescent, or at least sufficiently quiescent to let them maintain a fairly normal existence.

Steroids were introduced into the treatment of colitis about 1950 and have been

Dr. Tumen, diplomate of the American Board of Internal Medicine, specializes in gastroenterology and is Chairman of the Department of Medicine and Professor of Medicine in the Graduate School of Medicine, University of Pennsylvania.

used very energetically in some places since and with lesser degrees of enthusiasm almost universally. We now know, as a result of follow-up studies, approximately what these drugs do and have some idea about their value, even though a final evaluation cannot be given.

In so far as the type of therapy is concerned, the choice of drug, it is known that from the standpoint of getting a maximum steroid impact the best drug to use is ACTH itself. This is given intravenously in doses that range from 20 to 40 milligrams per day, given very, very slowly over a period of ten or twelve hours.

In those instances in which oral therapy is desirable and considered satisfactory, the earlier used hydrocortisone and cortisone have gradually been replaced by prednisone or prednisolone. The more recently introduced steroids have not been used sufficiently to permit any conclusions about them.

In so far as local use is concerned, recently, as you well know, there has been some enthusiasm for the local rectal use of hydrocortisone in doses of 100 to 200 milligrams by intra-rectal drip, given slowly each night, for a period of approximately two weeks. There are also suppositories that contain 10 to 15 milligrams of hydrocortisone that can be used two or three times a day. These have largely been limited in their use to patients who have the rectal type of ulcerative colitis, or at most rectal-sigmoidal, relatively mild disease and have frequently given results considered to be at least beneficial in this type of local disease.

The Word "Cure"

Much has now been learned about steroids. I have already indicated that we don't use the word "cure". We feel that by and large this is a suppressive type of therapy. We know that the disease is one in which steroids frequently give symptomatic relief, and sometimes very, very promptly, that is not paralleled by anatomic changes in the patient. In other words, the sigmoidoscopic picture lags behind, if it improves at all, and x-ray improvement may never occur, or if it occurs, it occurs infrequently and very, very slowly. We know that steroid therapy is adjunct therapy, that in no instance should it be used at the expense of discontinuing or failing to use the standard things that we depend upon—diet, supportive psychotherapy, sedative medication, the sulfonamides and the occasional antibiotics that are thought to be helpful. To rely on steroids alone is a very, very serious mistake. As I must say repeatedly, we also know that improvement of the patient from the standpoint of symptom control in no sense means that the patient is well of his disease or that follow-up observation of the patient can be discontinued.

Difficult Evaluation Of Results

From the standpoint of the choice of patient, or the indications for steroid therapy in ulcerative colitis, here again one sees varying enthusiasm in the selection of cases. In general, it is believed that steroids are of value in those patients who have acute fulminating colitis of maximum severity. Many people also advise that steroids should be at least tried in those patients who have recurring colitis that has been resistant to other forms of therapy. Many of us feel that if steroids are to be used at all they should preferably be used in those patients who are in their first attack of ulcerative colitis, in the hope that we can bring about a regression of the disease before it has produced major structural changes in the bowel. That, of course, makes it very difficult to evaluate the results of therapy because many of these patients do, and in the past did, get better without steroids, so that if improvement takes place, it may be fallacious to give the steroid therapy credit for relieving the patient.

There is also definite indication for the use of steroids in treating those patients who have some type of complication of

colitis; iritis, such as Dr. Gordon would be interested in, arthritis and erythema nodosum. In these patients the ulcerative colitis is probably part of a multiple system disorder such as the collagen diseases, the use of steroids is probably doubly justified. A good bit of work is being done in various institutions, particularly by Dr. Kirsner in Chicago, with the thought that many patients who have ulcerative colitis have this multiple system type of disease. He finds in the ground substance of the bowel changes that are very much like those that are seen in collagen disorders. Recently he has done some work in which he has found in some patients with ulcerative colitis changes in the gamma globulin of the serum which seem to indicate that in some patients there is a type of hyper-immune reaction. He has felt that in these patients, particularly, steroids are helpful and are indicated.

Few Contraindications To Use Of Steroids

The contraindications to the use of steroid therapy are relatively few. These include threatened perforation of the bowel, recognized perforation and peritonitis, and abscess formation. A few patients have what is now called toxic dilatation of the colon in which there is threatened perforation of the bowel, and in these also the use of steroids is contraindicated. It is now thought that major hemorrhage is not a contraindication. In these patients it is possible that steroids may be helpful.

The complications of steroid therapy have really been very few, aside from the systemic complications with which you are so familiar. The question of peptic ulcer as a complication of steroid therapy of ulcerative colitis has been widely discussed. For some reason, the incidence of peptic ulcer in patients with ulcerative colitis is definitely less than in patients who have steroid therapy for arthritis. Perhaps one or two percent of the patients get symptoms of ulcer, and in practically all instances these can be controlled by proper diet and antacids and steroids do not have to be stopped.

Perforation of the bowel has been reported in some patients who have been given steroids. I have seen it myself, but I must say I am not at all sure that the perforation of the bowel followed steroid therapy. The incidence of perforation of the colon is about the same in patients who were given steroids as in patients not given steroids. Perforations may therefore be a coincidence and not related to the use of steroids.

Psychotic Reactions Greater

The incidence of psychotic reactions to steroids has been definitely greater, I should say, in ulcerative colitis patients who are given steroids than in those given steroids for other purposes. In one large series that I know of, the incidence of psychotic reactions is reported to be as high as 15 percent. I should probably not use the word "psychotic;" I should say "emotional disturbances," because very few of these patients develop frank psychotic changes. These have generally been controlled by the administration of tranquilizing drugs and gradual stopping of the steroids.

One may say, therefore, that the contraindications to the use of steroids are few and that the complications are few, and that there is very little argument against using steroids, provided one is frank in admitting that the results of this form of therapy are not always as good as we would like them to be.

Now, what does steroid therapy do for the patient with ulcerative colitis? Well, today we say that it doesn't cure, but that it seems to initiate and potentiate recovery. Those are weasel words of the sort that we use in trying to cover a good bit of ignorance about the mechanism of relief in these patients. When we start steroid therapy in patients with active ulcerative colitis there is, in a very high percentage, from 70 to 80 percent, prompt relief of symptoms that is sometimes almost mir-

aculous. I have seen patients who have been on other forms of therapy so that we had an adequate control period and who were violently ill with all of the active symptoms of very severe and serious colitis who lost their symptoms in the sense of having a drop in temperature, a decrease in bowel movements, and cessation of bleeding practically instantaneously when intravenous ACTH was started. When one looks into the sigmoids of these patients, however, the bowel looks exactly the same as it did the day before, and we know that among this 70 to 80 percent who get symptomatic relief very promptly there very often is recurrence of the symptoms within a short time, even though the steroids are continued.

Danger Of Relapse

It is necessary to recognize this fact, that many of the patients whose symptoms are relieved by steroids go into relapse either while steroids are still continued or when steroids are stopped. In perhaps 60 to 70 percent of these patients there is a relapse within the course of a few weeks or a few months after steroids are discontinued.

In some patients, on the other hand, with whom we are particularly fortunate, the use of the steroids is gradually followed by objective evidence of improvement. Over a period of a few weeks there will be gradual improvement in the sigmoidoscopic picture. The mucous membrane becomes granular, bleeding and exudation decreases, the mucosa doesn't traumatize, and the patient shows this objective evidence of improvement.

In perhaps 30 percent of patients given steroids, accompanied by the other routine forms of therapy, there is a gradual improvement that is permanent over a reasonable period of time—in other words, during periods of follow-up that range up to two, three or even five years.

We also know, however, that when steroids are discontinued, in the majority of patients there is gradually a tendency to recurrence, so that the relapse rate even in those patients who have had long-continued steroid therapy is fairly high. There has gradually developed the idea that many of these patients in whom the disease can be suppressed should be kept on long-range steroid medication, and there are now reports of many individuals who have been kept for a year, two years, or even as long as six years on steroids. In about 30 to 40 percent of the patients who have long-continued steroid therapy, the disease is kept quiescent at least in the sense that the recurrences are mild, not incapacitating, and the patient is able to maintain a fairly useful life in much the way that many patients who have duodenal ulcer disease might have mild recurrences for a few days a year and not be terribly ill.

Our policy at present, therefore, is to say that since there are relatively few contraindications to the use of steroids in treating colitis, since we understand the complications, and since we can manage these in most instances, we use this form of therapy for those patients whose disease is in its early stages and also for patients who have moderately severe disease. We give it a trial of at least two or three weeks, not longer, because the result should be fairly prompt, to see whether benefit will occur. If it occurs, we continue steroid therapy for possibly two or three months. If during that period of time there is objective as well as subjective improvement, we gradually discontinue, very slowly by decrements of possibly 5 or 10 percent, the steroid that we are using. If the patient shows signs of relapse, the dosage is increased again. If the patient has continuing objective evidence of activity in spite of symptomatic improvement, we continue steroids for a long period of time, constantly observing the patient to evaluate his course and in the hope of avoiding some of the major disorders that occur. If the patient gets worse, then, of course, we are

faced, as we are in many instances, with the decision between continuing medically, including steroids, or resorting to surgery.

I think we find that the over-all picture of relief with steroids is probably not impressively greater statistically than with non-steroid therapy. In other words, we may have, instead of the 20 percent of patients who remained well before steroids, perhaps 30 percent. Instead of the perhaps 20 percent who remained not entirely well but not terribly sick without steroids, there may now be 25 or 30 percent, maybe a few more, in this category.

Guidance In The Selection Of Cases

We know, as I said before, that we are not curing many of these patients in the strict sense of that term. We feel, however, that it is impossible to select in advance the patients who will be benefited by steroids and those who won't be so benefited unless something comes of the work dealing with hyper-immune reactions and the gamma globulin changes that I have mentioned and which help in the selection of cases. We therefore feel that practically all patients with ulcerative colitis deserve a trial of steroid therapy, although when we see these patients who have been ill for long periods of time and have the terribly changed colons, the ruined colons that are so destroyed that we can say that the disease has reached its maximum impact, we have a definite feeling that in those patients we probably are making a gesture more for ourselves than in the hope that we are going to benefit the patient. We know that most patients deserve a trial of this type of therapy because we are dealing with a terrible disease; we are dealing with a disease we don't understand too well, and if we give these patients relief, then we have accomplished something, and we may avoid colectomy for some of these individuals. What is not known today is the long-range situation in the sense of many, many years of follow-up of the patients who have had steroid therapy for long periods of time. That we don't know. What happens to their colons, whether they will have a higher incidence of adenoma, whether more of them will develop carcinoma if we keep them going for long periods of time is unknown. Whether the steroids will maintain their effect indefinitely is also unknown. But at least there is enough clinical experimentation going on by careful observers so that we hope over a period of time to be able to answer these questions.

I think, however, that if we approach this problem honestly and say that this is a disease we don't understand, this is a disease in which we can't speak in terms of "cure," this is a disease in which steroids may help to suppress the activity and to give the patient a reasonable chance of continuing a normal existence, then this type of therapy does have a definite place, providing we recognize its nonspecific nature and limitations. I would say that this is a reasonable form of therapy to add to what we already do and which, in the final analysis, is not terribly specific anyhow.

When I turn to the question of using steroids in treating liver disease, what I have to say is even less conclusive than what I had to say about the treatment of colitis. Here we are faced with tremendous confusion because of the absence of universally accepted terminology and absence of complete understanding of etiology. We know little about the true nature of many liver diseases. We have two words that we use for almost all liver disease: hepatitis, when the disease is acute, and cirrhosis when the disease is chronic. But whether each of these terms covers one or many diseases is still quite unclear.

Steroids have been used for a long time in the treatment of various liver diseases. We know that these substances do not greatly alter liver function, as this is usually measured. They do increase the glycogen in the liver and they also increase the deposition of hepatic fat. What these changes mean in terms of liver function is

uncertain. Steroids also suppress inflammatory changes in the liver and, possibly, fibrotic changes, as they do in other types of organic disease.

One curious fact that has come to light is that steroid therapy is very often followed by a decrease in serum bilirubin of patients who are jaundiced. The mechanism of this is not clear. This has been seen in some patients who have mechanical obstruction of their biliary ducts but chiefly in patients who have hepatitis with either parenchymal disease or intrahepatic obstructive changes of an obscure nature.

False Signals

Unfortunately, the lowering of the serum bilirubin has often been thought to indicate improvement and when patients with jaundice due to hepatitis were given steroids and became less jaundiced it has been assumed that the steroids were curing the hepatitis, and that these patients were getting better more promptly than would have been the case without steroids. That is not so. If the steroids are stopped, the serum bilirubin usually rises again, the biopsies of the livers do not show subsidence of the disease, and liver function is not necessarily changed, so that steroids cannot be said to alter or change the course of the disease. Steroids are not now being used, therefore, in the treatment of the average case of acute hepatitis. They are still used in acute cases of fulminating hepatitis with rapidly rising jaundice and evidence of severe necrosis of the liver, if the patient is apparently lapsing into acute liver failure. In these patients we are often so desperate that we use steroids along with everything else, and it is thought that possibly in some of these patients the steroids may alter the course of the disease and help keep the patient alive. The fact remains that the only type of treatment that has seemed to be of any avail, and then only occasionally, in patients who have massive fulminating necrosis of the liver due to viral hepatitis has been steroid therapy. Whether the benefit has been coincidental or not I don't think one knows.

The Term "Chronic Hepatitis"

It is almost impossible to give a brief and generally acceptable definition of chronic hepatitis. This is one of those terms that includes a hodge-podge of patients, not only those who have continuing parenchymal disturbance following viral infection, but also those with continuing alteration of the so-called cholangioles of the liver and those with various types of hyper-immune reactions. Here again we are waiting for some Moses to lead us out of the wilderness of classification and this may help in the selection of cases of a specific type in which the use of steroids can possibly be more specific.

At the present time many of us use steroids in the treatment of those patients who have long-continuing jaundice, who seem to be gradually going into so-called biliary cirrhosis. It is possible that in some of these patients the steroids act to suppress the inflammatory and destructive changes in the liver and relieve the patient symptomatically. In the majority of such patients the disease process is not fundamentally altered by steroids. When these are stopped the disease seems very much the same as it was before. As is true in ulcerative colitis, possibly some of the patients who have the hyper-immune reactions that we now call lupoid hepatitis, the patients who have the type of liver disease that might be associated with some type of hypersensitivity change within the liver, seem more likely to be helped by steroids. Here these drugs seem particularly valuable in slowing down the course of the disease and in relieving symptoms. In these cases, the steroids can probably be continued for long periods of time with out hurting the patient and may benefit in the sense of keeping the disease quiescent.

Steroids are not used in the routine treatment of cirrhosis. Most steroids increase fluid retention. There is some

suggestion that they may increase the tendency to variceal bleeding, and by and large they have been abandoned, except that there has been recently some interest in the use of prednisone in the management of ascites in cirrhosis. It is thought that this particular type of steroid may increase water excretion and may possibly suppress the aldosterone mechanism, although I think that this is questionable. The opinion is held by some that if the use of prednisone is combined with restricted sodium intake, ascites is got rid of more rapidly in the cirrhotic patient than otherwise. We have some patients who have done quite well on this program, but this is something in which numerous control studies and a good bit of statistical analysis are necessary before we really will know the answer. We feel that there is no contraindication to prednisone in these patients with cirrhosis and ascites but we are not prepared to say that this is terribly helpful.

Finally, in hepatic coma itself, the end stage of the liver failure that occurs in so many different types of liver disease, steroids are now rarely used. This is particularly true when coma is the end result of progressive chronic liver disease such as cirrhosis. Reliance is placed on other forms of therapy and we have largely abandoned steroids as the shot in the arm type of therapy that is going to snap the patient back because it usually has no beneficial effect whatsoever.

The only instances of coma in which the use of steroids seems valid are those few instances that I mentioned already, those patients who have fulminating liver disease who are going into coma as a result of an acute toxic or viral injury to the liver. In those patients massive doses of steroids, up to 1,000 or 1,500 milligrams of cortisone a day, occasionally have been followed by recovery of the patient. I think it is important to emphasize how few cases have responded to this therapy and how difficult it is to reach a final judgment on the basis of these few patients. I would, however, certainly say that in this very desperate situation, in which the maximum type of therapy must be applied, there would be no contraindication to steroids and possibly in individual cases they may be helpful.

I am afraid, therefore, that I have to end my discussion of steroids in liver disease by indicating, as I did already, that this is an unfinished topic, that much remains to be learned, that by and large steroids have not been very helpful in treating hepatic disease, although occasionally they do help to suppress symptoms and possibly may keep the patient from a desperate situation.

I myself feel, as I have already stated, that our chief problem is one of accurate diagnosis, that we know relatively little about what goes on inside the liver, that possibly in the future we will be able to select individual patients or individual types of liver disease in which steroids will be helpful. As we define liver disease today, however, steroids seem to have very little part in its treatment and are not in any sense of the word curative or even helpful in most instances.

SYMPOSIUM

The second Hahnemann symposium on hypertension will be held at the College in Philadelphia on Thursday and Friday, May 4 and 5, 1961. Further particulars may be had from Albert M. Brest, M.D., Head, Section of Hypertension and Rhinology, Hahnemann Medical College.

THE USE OF STEROIDS IN ARTHRITIS

and Related Diseases

● **As might be expected, steroids have attained an acknowledged place in the treatment of arthritis, the disease under investigation during their development. Nevertheless, their use does not constitute the sole or even major portion of the treatment.**

JOSEPH J. BUNIM, M.D.

It is impressive how similar ulcerative colitis and rheumatoid arthritis are insofar as what can be said about the cause, the cure and the role of steroid therapy in these diseases.

I am grateful to Dr. Tumen for the remarks that he made because they will simplify my presentation considerably.

Rheumatoid arthritis has many similarities to ulcerative colitis. It, too, has a varied course and because of this it is difficult to evaluate the various therapeutic agents because there are spontaneous remissions, there are mild courses in some cases, and one is never sure how much one has contributed to the recovery or improvement of the patient as a result of any single therapeutic measure such as steroids.

Again, as in ulcerative colitis, we emphasize that steroids, when used, should certainly not be the only agent in the therapeutic regimen. This holds true for any anti-rheumatic compound, whether it is aspirin or gold or phenylbutazone or antimalarial agents or steroid therapy.

The indoctrination of the patient: orienting him as to the nature of the disease, the likelihood of its chronic course, the fact that it is rather foolish to look for miracles, an attempt to resolve some of his inner conflicts, to help him with emotional and other problems, and in addition to that, some rest from stressful environmental factors, corrective exercises, splints, casts, physical therapeutic measures—these are all very important in a comprehensive individualized regimen.

In addition to that, there are cases where steroids in properly selected cases are helpful. There is no doubt that despite the limitations and undesirable side effects, in some instances major catastrophic undesirable side effects, despite these there is a very definite place for steroid therapy in carefully chosen cases of rheumatoid arthritis.

There is another very striking similarity between the two diseases in that although we observe very impressive improvement subjectively and objectively and even insofar as laboratory changes are concerned as a result of steroid therapy, we nevertheless fail to alter the ultimate course of the disease.

When one compares the end results after ten years of experience, and in some in-

Dr. Bunim, diplomate of the American Board of Internal Medicine, is Clinical Director, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

stances after six or seven years of treatment, one is impressed that the end results are not strikingly superior, certainly are not spectacular. Although there is subjective and objective clinical improvement, there may not be anatomical improvement or arrest of destructive changes. Nevertheless we must not lose sight of the fact that the intermediate results in the intervening years during those eight years the patient had been able to return to a state of employability and lead a life worth living which he might not have been able to do had he not received steroid therapy.

The similarity between the two diseases goes even further than that. Some of the complications are common to both, such as iritis, which Dr. Tumen mentioned, and of course patients with ulcerative colitis, in a small percentage of cases, do develop arthritis which is indistinguishable from rheumatoid arthritis. They may even develop sacroiliac arthritis and involvement of the spine as well.

Further there is the point which Dr. Tumen made which Dr. Kirsner has emphasized of hypergammaglobulinemia and apparently an increased antibody reaction or responsiveness. This is very true of rheumatoid arthritis. The hypothesis of Dr. Kirsner is that perhaps this disease is, after all, an auto-immune disease, that the patient may become sensitive to some of his own tissue constituents, especially in the gastro-intestinal tract.

Two Striking Differences

We are toying with the same idea in rheumatoid arthritis, but we have not yet been able to even approximate the site of the antigen formation or even to tell whether it is an intrinsic or an estrinsic or endogenous or exogenous antigen.

There are two striking differences between the two diseases. One concerns the undesirable side effects of steroid therapy in rheumatoid arthritis, the formation of peptic ulcer (gastric or duodenal.) A disturbingly high percentage of such patients may develop severe gastrointestinal hemorrhage or perforation. And yet in a disease which intrinsically involves the intestinal tract, such as ulcerative colitis, peptic ulcer rarely occurs as a side effect of steroid therapy. This is rather ironic.

The second difference between the two diseases is that in cases of ulcerative colitis that develop arthritis clinically indistinguishable from rheumatoid arthritis one does not find the rheumatoid factor in the serum; that is the factor that is responsible for the hemagglutination reaction, (the sheep cell agglutination or the Latex fixation test or the bentonite flocculation test).

In all these serological reactions, which are rather specific for rheumatoid arthritis and occur in about 85 per cent of cases of definite rheumatoid arthritis—this reaction has never been found in patients with ulcerative colitis that develop "rheumatoid" arthritis.

Indications For Steroid Therapy

The indications for steroid therapy in rheumatoid arthritis I would say are somethink like this: We firmly believe and everyone agrees that steroids should not be the first measure to be used when the patient is first seen.

We believe in a very conscientious and earnest trial of conservative therapy, applying the various measures which I have already enumerated. The anti-rheumatic agent one should use first is aspirin, in one form or another, in adequate dosage and at regular intervals.

If, however, after months of conscientious and persistent, patient administration of such a conservative regimen the disease seems to progress rapidly and relentlessly and the patient is threatened with invalidism, disability or prolonged unemployment, one has to consider a more potent measure, and regardless of what measure one resorts to there is involved a definite, calculated risk, whether it be gold or phenylbutazone or anti-malarial agents or steroids. There is a risk, and one

should sit down with the patient and calculate the risk of the undesirable side effects on the one hand against a relentless course and unemployment or invalidism on the other. This is not easy to do.

The contraindications to steroid therapy in rheumatoid arthritis, are not as numerous as we had thought originally. I think the most important thing is a careful history and a careful examination before therapy is begun to make sure that certain diseases or complications do not coexist.

For example, it would be hazardous to miss the presence of active tuberculosis, because giving such a patient steroid therapy without the protection of antibiotic, anti-tuberculous therapy, might have serious consequences.

On the other hand, if the patient is really in need of steroid therapy and yet has tuberculosis, one may administer steroid therapy provided the patient is well protected with isoniazid or some of the other effective antibiotic agents.

The same holds true for other concomitant infections that are responsive to antibiotics. The danger is that such infections might not be recognized before or during the administration of steroid therapy. But having discovered the disease and armed with an effective antibiotic, steroid therapy is not contraindicated.

The same holds true for diabetes. There is no question that steroid therapy will reduce carbohydrate tolerance, and in a small percentage of cases (one to three per cent) may even cause steroid diabetes. Nevertheless, if a patient had severe rheumatoid arthritis and had diabetes, one would not hesitate to administer steroid therapy knowing the diabetes could be controlled with increased amounts of insulin or dietary adjustment.

Beneficial Effects

With this introduction, I would like to go on and talk about some beneficial effects of steroid therapy in rheumatoid arthritis, and also some undesirable side effects.

As you know, current usage is almost confined to the synthetic anti-rheumatic steroids. We rarely use cortisone and hydrocortisone now. The commonest analogs are prednisone, prednisolone, triamcinolone, methylprednisolone or dexamethasone. There is a definite correlation between the biological and clinical effects of these steroids and their chemical structure.

The difference between prednisone and cortisone is that there is a double bond between carbon 1 and 2. Prednisone is the analogue of hydrocortisone, again the same difference.

Triamcinolone differs more radically in that there has been added a fluorine in carbon 9 position, and in 16 carbon position an hydroxyl group.

Medrol is very closely related to prednisolone. The only difference here is that a methyl radical has been added at carbon 6.

Dexamethasone is related to triamcinolone with remarkable difference in side effects, and yet the only difference chemically between these two compounds is, instead of having a hydroxyl radical in the 16th position, we have a methyl radical.

The anti-inflammatory effects of steroids was clearly demonstrated in a patient, 17 years old who had rheumatoid arthritis for three years and had been getting aspirin regularly in fairly large doses. He was not responding, and we had decided to put him on prednisone. He was one of the first patients who received prednisone, back in 1954. A biopsy of the synovia of the knee at the time he was getting aspirin showed characteristic rheumatoid synovitis, and a very large purple area indicated fibrinoid degeneration; round connective tissue cells in an active stage of proliferation; a cluster of polymorphonuclear cells, and more significant, the absence of synovial lining. The lining was completely destroyed, and there were no deposits of lipid cells.

A biopsy of the same patient, the same knee 24 days after prednisone therapy was begun, showed a very different picture. A restoration of the intimal lining took place, the polymorphs disappeared; the fibrinoid degeneration was completely gone, lipid cells reappeared and there is no question that it indicates steroid a very effective and impressive anti-inflammatory agent.

Clinically we measure the effect by attributing arbitrary numerical values to pain, motion, tenderness, swelling — we measure the proximal interphalangeal joints with jeweler's rings, measure the range of motion, subtract from normal and get the deficit and measure the duration of morning stiffness. In a series of 24 patients, most of whom had been on other steroids and had stopped responding altogether, an impressive improvement was shown with the use of dexamethasone over a period extending from 4 weeks to a year and a half.

In our endeavor to constantly reduce the steroid dosage, we have supplemented aspirin. This measure is very effective in reducing steroid requirement.

Importance Of Dosage

There is no question in our mind that the single most important factor in reducing the incidence and severity of undesirable side effects in rheumatoid arthritis is dosage. As a matter of fact, we do not strive for complete suppression of symptoms for fear that we are paying too high a price by increased dosages. So we are willing to settle for sub-optimal control of the disease.

Now, there are some instances where this did not work. This column shows the amount of salicylates in grams per day, that was supplemented. In 50 per cent of the cases there was very effective reduction in the requirement of steroid. Here is a patient, for example, who required 4 milligrams of dexamethasone a day. This is the maximum dose we dare give to any patient. If he doesn't respond to that, then we feel he is not a patient for steroid therapy, and we rarely go as high as 4. One of the patients needed 4 mg. and yet on 3.6 grams of salicylates was able to do with one mg. daily.

Another had 4 and with salicylates was able to do with 1.5 mg. These are not just coincidental reductions in severity of the disease or remission because when we take them off aspirin these patients again require higher dosage.

To summarize, I would say that in 50 per cent of our patients we have been able to reduce the steroid dose by 50 per cent when we supplement aspirin.

Undesirable Side Effects

I am sure you are familiar with some of the undesirable side effects of steroids. Out of 27 patients 25 developed the cushingoid symptoms; 23 had reported severe increase in appetite, which was almost uncontrollable, and as a result 19 of our 27 patients gained at least 10 pounds, and many of them gained 20 and 30 pounds; 11 of our 27 patients had petechiae. Other less frequent symptoms were restlessness and insomnia. There were no cases of psychosis to our knowledge either in our Institute or other groups. Hirsutism, increased sweating and edema (this happened to occur only in patients who had petechiae), occurred in a number of patients. The mechanism for this edema is not yet clear and we wonder whether the integrity of the capillaries may not be involved. Epigastric pain developed in 4 patients. Fractures occurred in 3 of 27 patients. Only 1 of 27 patients developed hypertension, and he was borderline before steroid therapy was given. I wonder whether there isn't something encouraging about the low incidence of hypertension, of psychosis, in the newer synthetic steroids. This of course remains to be confirmed by greater, longer trial. Only 1 patient in our series had a peptic ulcer. We x-ray our patients (gastro-intestinal series) regularly every three months and only

found one with peptic ulcer. However, other observers have found higher incidence than 1 out of 27. It remains to be seen whether there is a true reduction in the serious undesirable side effects with dexamethasone, as compared to the older steroids.

Supression Of Thyroid Function

One of the physiological abnormalities or side effects that result, which is of little clinical importance, is suppression of thyroid function. The rate of radioactive iodine uptake falls as the dose of dexamethasone increases.

Dexamethasone does impair carbohydrate tolerance in a fair number of patients. Of the fifteen cases that we have studied carefully and on whom we have done repeated glucose tolerance tests intravenously, 5 showed a definite deterioration. One patient, before dexamethasone, had a normal glucose utilization rate and after 4 to 6 months of therapy was borderline. Another was borderline to begin with and clearly showed a diabetic curve. This person was normal pretreatment, again normal 4 to 6 months, by 7 to 9 months he had a diabetic curve.

So although glycosuria and hyperglycemia did not occur in these patients, judged where glucose tolerance tests were concerned there was a definite reduction in carbohydrate tolerance as a result of dexamethasone after several months.

The ulcer story is briefly summarized here. We have compared and drawn from the literature the incidence of ulcers in cases of spontaneously occurring Cushing's disease.

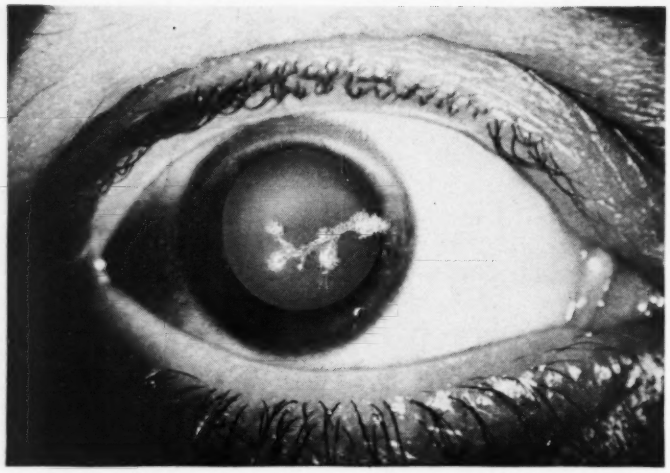
In the spontaneous Cushing's disease only 2 per cent of the patients developed ulcer; in patients with asthma, treated with steroids, the incidence varies from 2 to 8 per cent. In the control, subjects used by Dr. Kammerer, only 5 per cent had ulcer. In those who had rheumatoid arthritis but did not receive steroid therapy, 9 per cent. In those who did receive steroid therapy, 31 per cent developed ulcer. Dr. Ragan reported 26 per cent in a four-day study, of 68 cortisone-treated rheumatoid patients and we found 25 per cent in 60 cases on prednisone. I must add here that the cases that we treat and also I believe the cases that Dr. Ragan treated had severe rheumatoid arthritis and in many instances required high dosage.

Another undesirable side effect is compression of the vertebral bodies. The complications from compressed fracture are not severe. The patient is usually not disabled and there usually are no neurological complications resulting from compression of the vertebral bodies.

Finally, there is the problem of vascular lesions simulating or pathologically indistinguishable from periarteritis nodosa. A patient who had rheumatoid arthritis in a severe form had not responded to gold, salicylates or phenylbutazone. She was given steroid therapy and after four years of such she died of a disease clinically and pathologically indistinguishable from polyarteritis nodosa.

The incidence of vascular lesions in rheumatoid arthritis patients treated with steroids is greater than in patients not treated with steroids.

ANNUAL MEETING, Medical Society of Delaware
Wilmington, Delaware October 27, 1961



A drawing of dendritic keratitis (herpes simplex) under magnification—superimposed on a photograph.

I was interested in Dr. Flinn's remarks because after ten years of steroids we still find that most of the medical population know very little about them. I think that the very excess of talks on steroids has contributed to that situation.

When steroids were first introduced, there were many papers given regarding their use, despite the fact that the drugs were not available commercially. We had one program in New York in which the medical directors of Merck, Schering and Armour participated. I thought to myself, "Tonight I will get it from the horse's mouth, or the horses' mouths, and I'd better get there early because the place will probably be jammed." I went to the New York Academy of Medicine and found myself one of about fifty who were there. It was an excellent presentation. That night I learned something I had always thought about but had never known to be a scientific fact. A doctor from Yale gave a paper which proved that the most difficult event of the day was getting out of bed in the morning. I had always thought that was true, but it was a pleasure to have it confirmed scientifically.

I did learn a few other important facts, too. During the week I made it a point to ask a number of my medical friends why they had not been there that night, and each time the reaction was the same, "That is all you hear these days—papers on steroids." When I asked, "Have you been to one?," the answer was invariably "No, I haven't." The very availability of it kept them from learning how to use them because they figured, "Well, it is just another paper on steroids."

I had an exhibit at the American Academy of Ophthalmology two weeks ago in Chicago. It was a very simple exhibit on the therapy of uveitis. I have written about it as have others. I thought everybody knew all about it. The result was that I could not work up much interest and didn't have my exhibit ready until about ten days before the meeting. It was a "one-shot" affair which used mounted pictures. The exhibit got there with all the panels wrong and had to be changed. I was going to have five hundred reprints

†These informal notes were edited from a tape recording of Dr. Gordon's talk.

Dr. Gordon, a diplomate of the American Board of Ophthalmology, is Assistant Professor of Ophthalmology, at Cornell University School of Medicine.

● **Saving an eye may be almost as important as saving a life. One must first know the proper indication for steroids and then use them in ample dosage.**

STEROIDS IN OPHTHALMOLOGY†

DAN M. GORDON, M.D.

available and decided at the last minute to have a thousand. We ran out of reprints after two days of a four-and-a-half day meeting. I have had over two hundred requests for information left at the exhibit which I must answer.

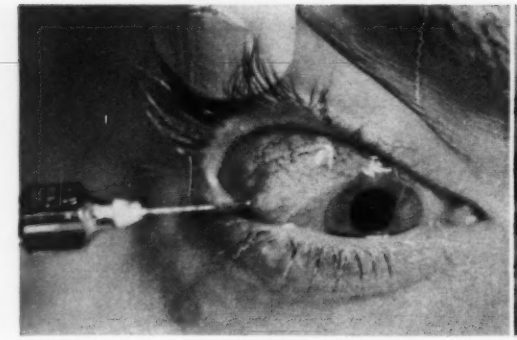
I have had a number of phone calls, including one yesterday from California, asking me how to treat patients. As an example, one patient had had a severe uveitis in her only eye since May and by the third day of her treatment, the internists had been hammering at the ophthalmologist about treating the patient too long with steroids. This gets back to some of Dr. Flinn's remarks. If the price is high enough, you treat them as long as they have to be treated. The price in this patient's case may be blindness.

I have a jet pilot in the New York Hospital at this very minute whom I saw for the first time one day this week with a choroidal lesion in the macula of one eye. He has to have binocular vision in order to maintain his job and for the safety of the passengers who fly with him. I am giving him intravenous ACTH, and starting with the second day of therapy, the internist became concerned about this "intensive steroid therapy." I wonder where these fellows have been during all of these ten years of lectures and articles and whether they even attend or read them.

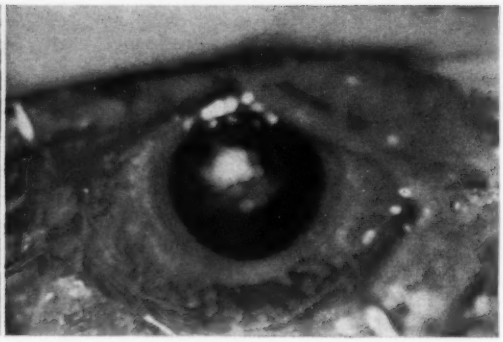
In the field of ophthalmology, steroid therapy has revolutionized the treatment of disease. I am fond of saying that steroid therapy is the guest who came to dinner with arthritis and stayed the weekend with ophthalmology. I don't pretend to know anything about the rest of medicine, but I do know what it has done for my field. We have been using it or not using it, or abusing it or not abusing it, without knowing why.

Three Important Factors

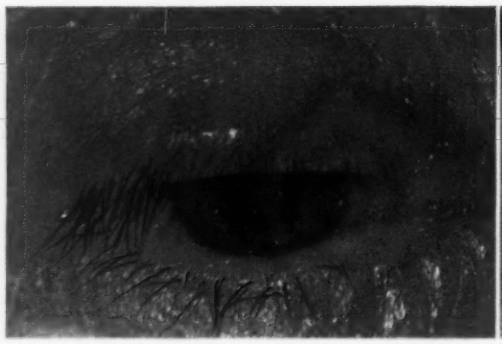
There are a number of important factors which I hope will come out this morning. In ophthalmology there are at least three important points to bear in mind. One is to know the indications and contraindications. The second is to use the proper route of therapy. The third is to use enough to do the job that you want to do. And if you are not going to use enough, don't use any. I believe that, within limits,



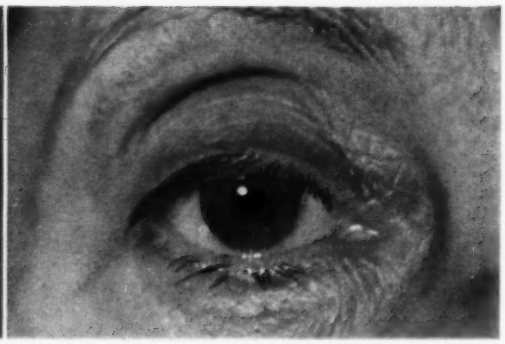
Technique of sub-conjunctival injection



Herpes Simplex of cornea—major contraindication to local steroid therapy

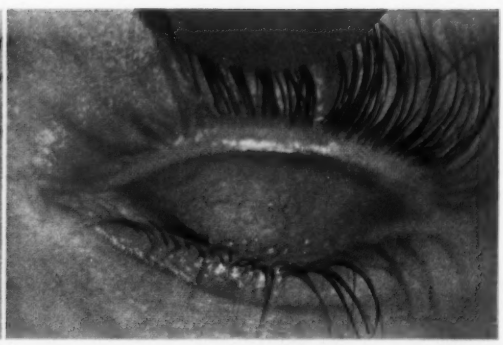


Severe ocular allergy before treatment



Severe ocular allergy after systemic and topical steroids

Vernal conjunctivitis before treatment



Vernal conjunctivitis after topical steroids

if you use inadequate amounts of systemic steroids in treating an eye disease, you feed the flames of the inflammation and make the patient worse.

The indications in ophthalmology are probably the same as the indications throughout the rest of medicine. There are exactly five: Inflammation, edema, allergy, the presence of granulation tissue, and certain infections. In these infections the concomitant indicated antimicrobial is mandatory. If the antimicrobial is not used, considerable difficulty may ensue. If used, it may save an eye which might not have been saved with an antimicrobial alone.

Local Contraindications

The local contraindications are corneal diseases, namely, herpes simplex, fungus, and some of the exanthemata. We believe that chicken-pox and small pox are definitely contraindications. I have had two cases of corneal complications during German measles, which responded to topical steroids. The most important single contraindication is herpes simplex keratitis. In those areas of the country where fungus is endemic, fungal keratitis is important. The human cornea reacts differently to drugs and diseases than do other parts of the body.

I will illustrate these indications and contraindications as we go along, and that will be the body of my paper. I think we can learn how to use steroids by learning why we make mistakes.

The route of application in ophthalmology is extremely important. If you can look at the lesion with your naked eye; in other words, if it is on the lids, conjunctiva, cornea and perhaps in the iris, you can probably reach it with topical therapy, that is, with drops and ointments of steroids, or steroids and antimicrobials.

If you can't see it with the naked eye, and that is in about 40 percent of the cases of iridocyclitis and in every case behind the iris, (that is, all choroiditis and optic neuritis) you must use systemic therapy. Eyedrops will not reach in, in clinically demonstrable amounts, if the lesion is behind the ciliary body.

The Purpose Of Treatment

The time to start treatment is when you make the diagnosis, because the purpose of treatment is to suppress the disease until the pathogenic mechanism burns out. While the etiology may be unclear, most eye diseases run a certain course. If the eye can be kept intact until it runs its course, the patient's therapy will be successful. The choroid and retina do not regenerate so that damage is permanent. I am one of those agnostics who do not believe in the survey method of treatment of uveitis. We do not know what causes most cases of uveitis. We waste a lot of the patient's time, money, and unfortunately sometimes his eye, in a long survey to try to find out what caused the disease. I have no objection to anyone looking for the cause, but I do object strenuously to making the eye forego treatment and suffer irreparable damage until such a time as the etiologic survey has been completed. Start treatment the moment you make the diagnosis. There is no such thing as a "course" of therapy. A course of therapy is enough to do the job that you want to do.

About six weeks ago, one of my patients had a cataract removed in his only eye. This was a young man in his twenties who lost his other eye with a Boeck's sarcoid uveitis. I have treated the remaining eye for ten years with systemic steroids. During this time the only demonstrable side effect was mooning and some slight water retention. Other patients, will show this same thing in a few weeks, or some in even a few days. Fortunately in ophthalmology most of our patients are healthy patients with a sick eye. In rheumatoid arthritis we deal with sick tissues and the story is different, just as it was different before steroids, when these patients developed many complications, now blamed on steroids.

I have a number of patients whom I have treated for more than six to twelve months, and up to eight, nine and ten years. I believe, and know, that where some steroids fail, others in equal amounts will succeed. When one steroid fails in what I presume to be an adequate dosage —somewhere between eight and twelve tablets, or intravenous ACTH running 12 to 16 hours, (not 5 hours) or intramuscular ACTH, which is used as an ambulatory procedure up to 200 units, (usually between 80 and 160 initially) I try a different steroid. I talk big dosages and use them because I believe that we need them in treating eye disease.

I find that where one steroid has failed another will often succeed. I never substitute prednisone for prednisolone, or vice versa, because they are too similar but I will substitute Decadron, etc., or any of the other steroids that we use.

I usually use triamcinolone when the patient has gained a lot of weight and I want him to lose water and weight—especially weight. In the absence of specific therapy, we employ steroids. When the cause of the disease is known and specific therapy is available it should be utilized.

The next point is very important. Never abruptly discontinue steroids without tapering off after you have treated a patient for approximately two or three weeks. If something happens that makes it imperative to stop quickly, the patient should be given a subconjunctival injection of a half cc. of 2½% cortisone, or its equivalent, in a suspension of another steroid. That may prevent a rebound phenomenon.

Most of the eyes with chronic uveitis cases which I have lost have been due to the development of a rebound phenomenon. The patient either went to a doctor who said, "Are you on that horrible stuff?" and immediately stopped treatment, or for some other reason the patient ran out of the drug and didn't bother getting any more and the eye was lost. A rebound phenomenon must be avoided at all costs.

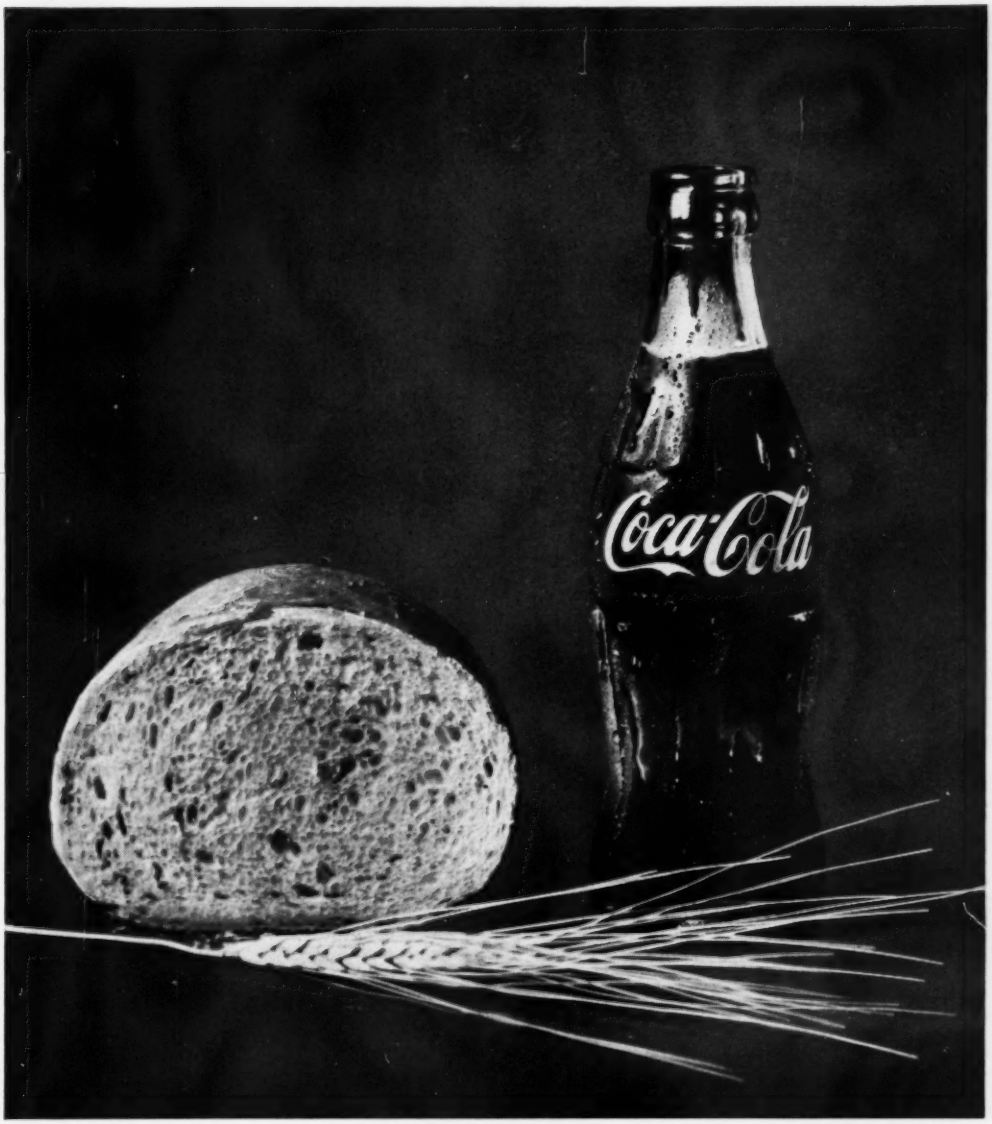
In a case which requires the method of subconjunctival injection, the injection is never given this low although I had to do it in one case for purposes of photography. I always inject high up under the upper lid so that the material is not visible cosmetically. This can be repeated every 3 to 7 or 14 days, as often as is necessary dependent upon the patient's clinical response. I have had some patients who have received as many as 75 injections. I have a number who have had two or three dozen. I have never had a serious consequence from these. However, if the patient is one who may require intraocular surgery within a few months, I would not inject in the area above where most ophthalmologists make the conjunctival incision because it will tend to glue the conjunctiva down. I would inject elsewhere.

This is a good procedure where steroids are contraindicated systemically or where the amount of steroids required systemically will jeopardize the patient's safety. The patient's physical well-being is paramount. Often by using subconjunctival injections the amount of systemic steroids needed can be markedly reduced.

Herpes Simplex (Illustration)
Chief Contraindication

The illustration of herpes simplex shows the chief local contraindication to steroids. Notice the branching lesion. Whenever you get a patient in whom the corneal light reflexes are irregular, you have reason to feel that there is something wrong with the patient's cornea. If the patient's corneal sensitivity is tested with a wisp of cotton and the eye is hypesthetic or anesthetic in contrast to the other normal eye, there is reason to feel that herpes simplex keratitis is present. Here steroids are withheld until the presence or absence of herpes simplex keratitis—so-called dendritic keratitis—is confirmed.

The fear of herpes simplex is not a reason for withholding steroids if reasonable precautions are taken. One, is to examine



Coca-Cola, too, has its place in a well balanced diet. As a pure, wholesome drink, it provides a bit of quick energy ... brings you back refreshed after work or play. It contributes to good health by providing a pleasurable moment's pause from the pace of a busy day.

DRINK
Coca-Cola
TRADE-MARK ®

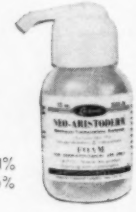
YOUR CHOICE OF FIVE TOPICAL FORMS

Neo-Aristoderm®

Foam Neomycin–Triamcinolone Acetonide

7.5 cc. and 15 cc. push-button dispensers

Neat, not messy or sticky—spreads readily without irritation or burning—for oozing, crusted, severely inflamed and injured skin or mucous membranes.



Each cc. contains:
Aristocort Triamcinolone Acetonide, 1 mg. . . . 0.1%
Neomycin Sulfate, 5 mg. 0.5%

Precautions: Contraindicated in herpes simplex. Sensitivity reactions to neomycin occasionally occur.

Aristoderm®

Foam 0.1% Triamcinolone Acetonide

7.5 cc. and 15 cc. push-button dispensers

Precautions: Contraindicated in herpes simplex

Aristocort

Cream 0.1% Triamcinolone Acetonide

Tubes of 5 and 15 Gm.

Precautions: Contraindicated in herpes simplex.

and allergic skin conditions . . .
simple, sparing application – prompt, symptomatic relief –

Aristocort®

Triamcinolone Acetonide

topicals

HIGHLY ACTIVE WHEN DIRECTLY APPLIED TO SKIN LESIONS

A recent study has demonstrated the efficacy of triamcinolone acetonide 0.1 per cent in 222 patients with a variety of allergic and inflammatory dermatoses. The conditions included in the study were contact dermatitis, seborrheic dermatitis, neurodermatitis, atopic dermatitis, and pruritus vulvae.

The anti-inflammatory and antipruritic efficacy of triamcinolone acetonide was shown by the prompt control of itching and resolution of affected areas. Cahn, M. M., and Levy, E. J.: A Comparison of Topical Corticosteroids: Triamcinolone Acetonide, Prednisolone, Fluoromethalone, and Hydrocortisone.

Antibiotic Med. & Clin. Ther. 6:734 [Dec.] 1959.

Aristocort
Ointment 0.1% Triamcinolone Acetonide

Tubes of 5 and 15 Gm.

Precautions:
Contraindicated
in herpes simplex

Neo-Aristocort®
Eye-Ear Ointment 0.1% Neomycin–Triamcinolone Acetonide

Tubes of ⅛ oz.

For inflammatory, allergic, infective eye and ear conditions

Each gram contains:
Aristocort Triamcinolone Acetonide . . . 1 mg.
Neomycin Sulfate . . . . . 5 mg.

Precautions: Contraindicated in herpes simplex. Sensitivity reactions to neomycin occasionally occur.

Lederle

LEDERLE LABORATORIES
A Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York

the eye with good magnification and a good light. The second is to test for corneal anesthesia before any corneal anesthetic is put on the eye. And the third is that every general practitioner and internist who examines an eye should learn how to use fluorescein, to stain a corneal lesion. If a branching lesion such as I have just shown you is present, steroids are not employed in topical therapy.

Five Indications For Topical Steroid Therapy

The first of five indications for topical steroid therapy is seen on a patient with an acute catarrhal conjunctivitis where the reflex from the light was clear and regular. If you find an irregular reflex on the cornea with your light, you have reason to feel that you have a distorted corneal surface and something is wrong. Test the sensitivity of the cornea and stain it with fluorescein. After treating this patient for five or six days with a combination of dexamethasone and neomycin, improvement was shown.

In a patient with proved APC conjunctivitis—the adenopharyngeal conjunctival form of viral infection—he responded to topical Decadron very beautifully. We have been seeing a number of these in the last few weeks. During an epidemic of sore throats there is a great deal of systemic virus disease around and patients always give a history of present or recent sore throat. Often we see tiny hemorrhages in the conjunctiva. Whenever a patient is seen with conjunctivitis, one should reach in front of the ear for a preauricular node. These viral conjunctividides practically always have an enlarged preauricular node, as well as marked edema of the upper lid.

I would like to discuss the case of a man who had an episcleritis. Episcleritis resembles conjunctivitis, but if the red area is palpated through the lid, it is very tender in contrast to conjunctivitis which is not tender. Episcleritis is usually red and localized to one quadrant of the external eye. One of the very few patients with episcleritis whom I have treated, did not clear up with topical steroids alone but required systemic therapy before he responded.

I might at this point say that most of the failures in treatment with topical steroids, where these are indicated, are due to the fact that most of us have gone to medical school and fallen into this t.i.d. or q.i.d. trap. Given an unlabeled pill or eyedrop, or what have you, one can usually assume that if it is given to the patient three times a day or four times a day, he will probably not drop dead. We fall into this same trap when we use eyedrops. We routinely instill them three times a day or four times a day. But when treating a disease, the goal is to saturate the lesion with the medication. In ophthalmology, three or four drops a day in an acute situation are usually insufficient.

Therefore, during the first day or two of treatment of any red eye which demands steroids, one should give the drops every fifteen minutes—or every half hour to every hour—the first day or two. Then when the eye responds, the interval can be increased between applications. Don't fall into this t.i.d. trap!

The same man after about three weeks of systemic therapy did very well. He had, I think, two recurrences about a month or two apart, and each of these responded although systemic therapy was required. Topical treatment was insufficient. When topical therapy in an acute situation does not work within 72 or 96 hours, or when systemic therapy in the amount employed does not produce a demonstrable response within that same period, it is necessary to increase the dosage. Having given it a fair trial of another three days, (say, on the increased frequency) if the disease still does not respond then try alternate preparations. That is the cue in an acute situation.

In a case showing a severe ocular allergy —with marked edema, crinkly appearance, and redness of the lids—the patient, surprisingly enough, had been taking ACTH

for a retinal condition. Often the systemic therapy will not affect the inflamed conjunctiva or lids, appreciably. When this occurs, the addition of topical steroids may produce excellent response—as happened here. About ten days later, there was an excellent response. Hence when the patient is using systemic therapy and you still have a red eye, add topical steroids.

While treating an intra-ocular inflammation, as a uveitis with combined systemic therapy and topical therapy, when decreasing the amount of systemic therapy, increase the amount or the frequency of topical therapy to cover the disease in case the systemic dose has been decreased too rapidly. The common mistake in treating many eye conditions with combined systemic-topical therapy is to decrease both simultaneously. One does not run into trouble with topical therapy as a rule, as it causes no systemic side effects.

In a young boy with vernal conjunctivitis or catarrh, pavement blocks appeared on the upper lid. This boy's father was a drug retail man, hence the boy had run the gamut of every form of therapy which was in the hydrocortisone days, prior to coming to me. About three weeks later, all the pavement blocks had disappeared but complete disappearance is not necessary for an excellent clinical result. The discharge stops and the maceration of the cornea ceases. Most of these children will lose their symptomatology when they get into their teens—a few will not.

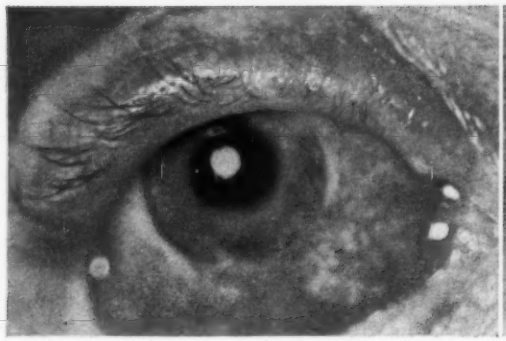
Lytic Effect Of Steroids

One of the first facts known about steroids was their lytic effect on granulation tissue. Yet for some reason we haven't taken advantage of this in ophthalmology. A child on whom I have done three squint operations before—finally getting him to where he looks pretty straight—developed masses of granulation tissue over the suture areas.

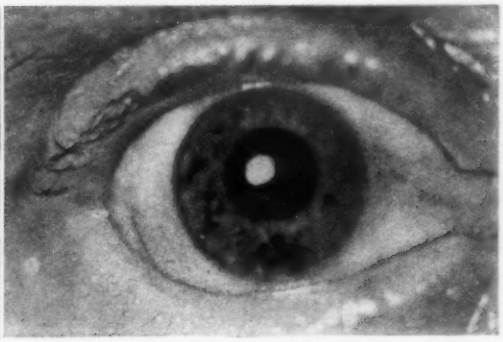
The same eye after about six weeks of Decadron ointment, shows improvement. He lost all of the granulation tissue. Normally this would have necessitated excision. When dealing with a child of three or four or five, a general anesthetic is indicated. I have never had to excise granulation tissue from this or any other cause since employing topical steroids, which do have a lytic effect upon granulation tissue and recent adhesions.

In localized areas of conjunctival injection, be suspicious of episcleritis or angular conjunctivitis—both of which are much redder. This form of localized injection should make you look for a foreign body or ulcer on the cornea. Along the limbus one can see this gray infiltrate which is the so-called limbal or catarrhal ulcer. It is the nicest form of ulcer to treat because it is not malignant, is always on the limbus and often associated with an acute catarrhal conjunctivitis. The patient in this case responded very beautifully to a steroid-antimicrobial combination. Prednisone 21 phosphate and neomycin was used, producing an excellent result.

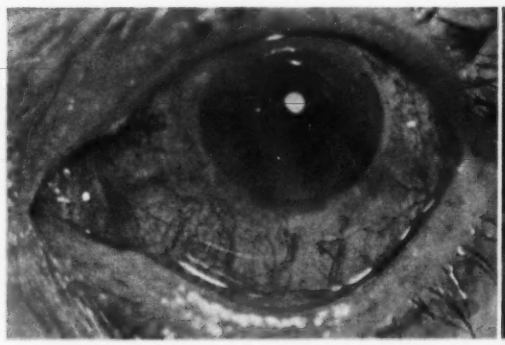
A pharmacist who came to me with an acute meibomianitis, had one draining lesion and another as yet unlocalized. This is the type of infection which usually necessitates incision and drainage. The infection localizes, leaving one or more small cysts in the lid which we ophthalmologists call chalazions. That is what happened in this case. I gave him a thousand milligrams of novobiocin the first day only and topical Decadron and neomycin every 1-2 hours. About four days later it had virtually all cleared up. Two days later all of this was gone, and he did not require an excision. He had a recurrence about six weeks later and he again responded to the topical medication. About that time I read about some work in England where antibiotic ointments were applied inside of each nostril for about six weeks twice daily in patients who get recurrent styes or meibomitis. The same medication was tried on this man. I have tried this on about a half dozen patients with recur-



Acute iritis before treatment

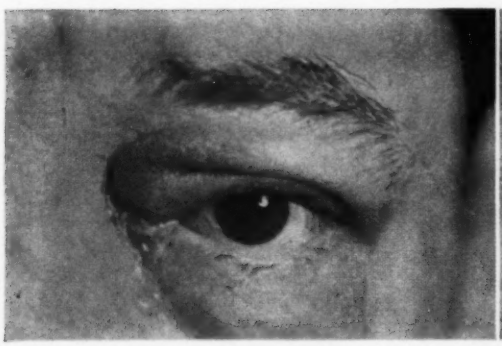


Acute iritis two weeks after systemic and topical steroids

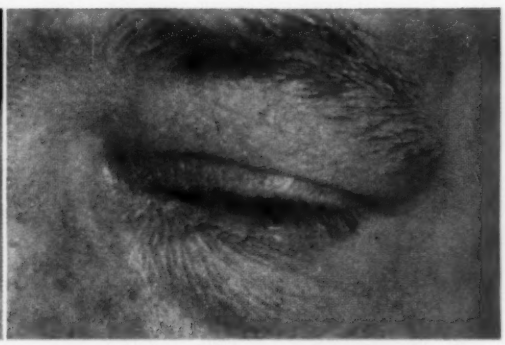


Acute glaucoma secondary to uveitis before treatment

Acute glaucoma secondary to uveitis after steroids plus surgery



Acute meibomitis (internal stye) before treatment



Four days after a topical steriod-neomycin combination

rent styes, and it seems to help in preventing recurrences. Whether they were lucky or whether the theory that the germs are picked up from the nostrils and carried to the eyes is correct, I don't know.

One of my patients was a "do-it-yourselfer" who plastered a ceiling and got some plaster in his eye causing rough corneal reflexes. When I threw a flashlight on this eye I saw broken reflexes, indicating that there was something wrong with the cornea. Normally the cornea will bounce light off in the same manner as a mirror unless its surface is disturbed.

In these cases one must irrigate the eyes copiously after first instilling a topical anesthetic. All particles must be washed out or lifted out with forceps or a moist Q-tip. One cannot chance leaving a single drop of plaster because it will erode the cornea. This man was treated with topical Decadron and neomycin ointment, applied frequently. In a picture taken ten days later, his condition was still not quite cured, but the cornea was clear and the final result was excellent. In any type of burn of the cornea, steroids are definitely indicated, preferably in combination with an antimicrobial.

In An Acute Inflammatory Disease

My plan of treatment in an acute inflammatory disease is to hit the disease as hard as I can initially. A patient with an acute intraocular inflammation may recover when untreated or he may go blind, but it is safer to treat him. If one stops abruptly, he may get a rebound phenomenon. Then, one starts again and suppresses the disease, after which one slowly tapers down. Do not be in too much of a hurry, but taper slowly until all medication is discontinued as long as there is no rebound. In patients with an acute iritis, who were treated on topical therapy alone, the response was excellent.

The first patient whom I treated on systemic Decadron was a young girl. I did not use atropine routinely, by the way. This girl who was referred by another ophthalmologist, had been taking prednisone for two weeks and was rapidly getting worse —showing marked ciliary injection. She had fibrin in the anterior chamber. I gave this patient less than the equivalent amount of Decadron and she promptly responded. About three weeks later, she practically recovered. This illustrates the fact that one steroid will work where another won't.

In a patient who came in with an acute glaucoma and a severe uveitis of some weeks duration, the increased pressure did not respond to therapy. About two weeks after surgery, the steroids were used topically and systemically. The very pale eye would have been red for weeks without steroids and probably would have been lost.

In A Chronic Intraocular Disease

My plan of treatment in a chronic intraocular disease is similar to the treatment of an acute disease excepting that decrements are made every two or three weeks instead of every several days and they are slow and guarded. We always try to find the minimum amount of therapy which will control the patient's inflammation and yet be compatible with his physical safety.

A patient who was seen by two eye doctors making a diagnosis of uveitis and retinal detachment because they thought these vitreous folds were detachments, was told, "You have uveitis. When the uveitis gets better we will treat the detachment." She was not given any therapy. She went to another ophthalmologist a month later and was then referred to us. I first gave her Deltra and then Medrol. After two months she made an excellent response. This lesion happened to be away from the disc and macula, so that the patient regained normal vision. If this patient had been treated with steroids promptly, the lesion would not have been this large. I know that she would have responded much more rapidly because a year later she had another systemically similar lesion and re-

sponded to steroids within a week. But she was given no therapy on the earlier occasion and this is what very often happens.

A lady of 70 was sent down from Massachusetts, after being treated for six months with two prednisone tablets a day. She rapidly became worse. She showed me how much money she had spent in that period on pills and it was a considerable sum. I treated this lady for nineteen months. In the hospital she was given intravenous ACTH; following which she made a good response and was sent home taking prednisone. She relapsed and came back into the hospital where she was given ACTH for a month. She did well and was sent home taking triamcinolone. She did all right for some weeks and then developed muscle weakness. Finally when I started working with Decadron—I tried her on that—she promptly responded after nineteen months of treatment. You can see the nerve easily now. The lesion which was high up where it could not be completely photographed had a small point reaching into her macula. Despite this, she came out of all this with 20/40 vision, which was excellent, and she tolerated the steroids well. When steroids were discontinued she developed some joint pains, which disappeared on 2 tablets a day plus some aspirin. This was very slowly withdrawn and she is fine now. She was in about a month ago, having been off medication for somewhere around six or eight months, and is well.

In a lecture I gave in neurology, I showed a slide illustrating a small vesicular lesion on the penis, similar lesions on the inside of the mouth, and a severe uveitis. No similar case in the literature has ever been successfully treated. The patient in this case was treated with intravenous and then intramuscular ACTH in doses of around 160 units a day, for almost two years, successfully. Then, since he was beginning to resemble a pin cushion, I had him hospitalized in his home area and they promptly discontinued therapy. He had a fantastic rebound, one eye had to be nucleated, and the other was so bad it too was lost. This is what happens. One should not stop when blindness is the price. This man developed an osteoporosis, one of the only three I have had—the other two patients are over 70 where the natural incidence is high, anyway. I think that if you ask the patient, "Which would you rather have, a fracture or your eyes," I think he will choose vision. You may have to pay the price, perhaps. And in most of our cases we have not yet had to pay any price for saving their eyes.

The presentation of this material has been made possible by a grant-in-aid from Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

ERRATA

The following errors appeared in Dr. Ruggieri's article, "Hemolytic Anemia in Typhoid Fever" in the March issue:

The table on page 78 should follow the paragraph at the bottom of column one, page 79. The list of studies appearing there should come after the paragraph at the top, ending . . . "were as follows." The 22nd line of paragraph 2 on page 80 should read *period*, not *second*.

The Journal regrets these mistakes.

PANEL DISCUSSION on the Use of Steroids

LESLIE W. WHITNEY, M.D., Moderator

DR. WHITNEY: We will now proceed with the panel discussion. I would like to have this conducted in an entirely informal manner and I will start the questioning with Dr. McGee.

DR. MCGEE: I should like to express my gratitude to the men who have come here to serve as panel members and point out that they differ from some of those who answer questions on notorious television quiz programs in that all of the members of our panel, in their formal presentations, were able to say "I don't know" or "We don't know in this area."

To Dr. Whitney I should like to express congratulations for his having arranged this fine panel and bringing us the opportunity that we have had this morning.

At the risk of over-simplification, I should like to try to pull together a clinical concept of what we may do to help patients with the materials that have been discussed this morning.

Let us take a period of five to seven days, one of several weeks, and then one of months (drawing on blackboard the three headings just enumerated). Then let us take a look at what was referred to by all of the speakers in connection with the anti-inflammatory effects of the corticoids. In each instance there was reference to a critical point. Whether the inflammation involved the eye, whether it involved the liver, whether it involved the synovial membrane of a joint, or was ulcerative colitis, there were critical points and examples shown.

The Search For "Antiphlogistic" Therapy

Our forebearers in medicine had a name for it. They were searching for "antiphlogistic" therapy in their patient. We have now a handful of exceedingly useful antiphlogistic agents. These agents have stood out when their application had to do with an acute inflammation, whether it was on an allergic basic or due to toxins, chemicals, infection or hyperimmune reactions in the body in the presence of certain disease processes. In all of these acute processes the anti-inflammatory effect can be life-saving.

It is fortunate that in this area of short term treatment the antiphlogistic action of the steroids does not bring us into the risk of undesirable hormonal effects, Cushing's syndrome or other. For pharmacologic effects in contrast to hormone or endocrine effects, we have an amazing range of dosage which we can use safely for this five to

Dr. Whitney, Moderator of the Panel, was Chairman of Committees on Meetings and Postgraduate Instruction, Delaware Academy of Medicine, and presided at the meeting.

seven day period. We can increase it many fold over hormonal doses in most instances and in getting this anti-inflammatory reaction one wants to be sure that the dose is large enough. In the presence of infection one must add antibiotic therapy for the underlying disease process, e.g., in tuberculosis, gram negative rod septicemia, and so on. For all of these acute infectious processes we do not have a specific therapy, but where one is recognized it is essential that antibacterial agents be combined with the steroids.

With massive short term steroid therapy it appears possible occasionally to save an eye, save a liver or save a life from death by anaphylaxis. We can use tremendous doses if we will combine the specific therapy with the non-specific pharmacological effects—I am not talking about hormone effects or replacement therapy in this zone. If we are able to stop steroids after a few days, we are staying out of trouble.

Watch For Complications

If we get into this second time zone of several weeks we have to watch for the complications related to the therapy. An example is the likelihood of reactivating a duodenal ulcer. And certainly over the months of steroids the "cushingoid" effects are a price of steroid therapy. In this area (indicating column headed "Months") we need much more knowledge. I believe all the panel experts felt happier with the acute short-term uses, and the benefits, than they did in the chronic or long-term uses. Possibly we will learn that there are steroid derivatives to be discussed, natural or not, that may do a little better job with certain disease processes and cause less unwanted reaction with prolonged treatment. We have to find out more of the actual end results, as is beautifully illustrated in the problem of arthritis, so to balance the hazards of complications against the accomplishments of steroids.

Recognizing these time zones makes it easier for the clinician dealing with the problem to recognize the patient's needs. I would emphasize that point. There are many disease processes that present no serious acute phase, do not threaten the patient, because the patient's own tissues handle the inflammatory reaction sufficiently well that there is no place for antiphlogistic drugs.

I would ask one question of Dr. Tumen and others who might want to comment on it. In a seriously inflamed liver, say of acute viral hepatitis, the clinician may decide that something must be done to arrest the worsening of the patient early in the course of the disease, and Cortisone or a derivative is started, for its therapeutic effect, and the patient improves. When the steroid is discontinued the patient worsens, and one may have to go back to it. It may be weeks or a few months before one can safely discontinue the therapy. Is that a rebound phenomenon or is that the nature of the disease process which would have killed the patient in the acute phase if suppression of the progress of disease had not succeeded under the large amount of Cortisone given for its pharmacologic effects?

DR. WHITNEY: Thank you, Dr. McGee. Dr. Tumen, would you like to comment on that question?

DR. TUMEN: I think that it is difficult to speak about short-range therapy in these patients. The emergency that exists in an acute liver disease or ulcerative colitis may be of short duration but the underlying disease process is not. I think that when one begins therapy in a patient in whom there is an emergency such as you describe, we are dealing with an overwhelming metabolic disturbance and the failure of an organ, in this instance the liver, that takes part in a tremendous number of metabolic processes. The breakdown of various enzyme systems is not well understood. I think that we may tide the patient over an acute emergency that might actually kill him, but the disease process takes a long time to subside and the organ takes a long time to come back to normal.

Certainly steroid therapy for these patients is not specific therapy. The term "antiphlogistic" is not a specific term. It applies to a general, vague, anti-disease type of therapy that we really can't explain in very specific terms. If the patient survives, it is extremely difficult to say our therapy, or any specific form of therapy, brought about survival. The patient has overcome an emergency. I think very often in the treatment of an acute liver emergency therapy is not directed toward treating the specific disease entity so much as keeping the patient alive. If during that period of time his own regenerative processes are sufficiently good to permit a vital organ like the liver to come back and begin to take part in all these various metabolic things, then he may survive. Since the liver is an organ that has a tremendous regenerative power, eventually he may recover completely.

The Question Of "How Long?"

I for one find it very difficult to say specifically that steroid therapy does that or contributes to it. I think we use it sometimes in desperation. I think we use it sometimes because we think that we should give the patient every possible benefit, just as we do many things in medicine. Because we can't evaluate what each thing does, we say, "Well, this is something that may help." We don't feel it does any harm, as you indicate, for a short period of time. We will try it. The patient survives, let us say, and we hope he does. Then we are faced with the decision as to how long therapy should continue.

I think under the circumstances that you describe, it is better to continue with therapy for a long period of time, over a period of weeks, then gradually taper off rather than stop abruptly. If the patient has a relapse when the steroid is discontinued, it is difficult to say whether the disease has undergone a remission because it is temporarily suppressed and is rebounding or whether it is a natural course of the disease. My own feeling would be that it is the natural course of the disease that is going on in most of these patients. I think that what we lack is the ability to select the cases in which the process will run its course and subside and those in which there is this low-grade smouldering thing.

What I have tried to say is that if we begin to treat these patients who have an acute liver failure we have to realize we are dealing with a non-specific type of therapy. I think that once we begin we should act as though we are treating something that may be going on for a long period of time. I think that during the period of prolonged therapy we can experiment with slow reduction to see whether there is a recrudesence of the disease. If there is, I think the tapering off process has to be very slow.

I think many times what is going on with the patient has nothing to do with the therapy. I think what is going on is a continuing smouldering disease that is going to go on and run its course whether we use steroids or not. The steroids may have the benefit in a few cases of keeping the patient alive during an emergency. Personally, I think that is rather rare in relation to liver disease. The steroids may have the effect of keeping the disease subclinical in some patient. I am not convinced that they contribute to a cure in the sense of having the disease disappear entirely. I think if the patient gets better, eventually, probably that is because he would have gotten better in any case.

I don't know whether that answers your question, but it represents a point of view about the use of these in liver cases.

DR. WHITNEY: Gentlemen, do you have any further comment about that? Dr. Lang, did you have a question?

DR. LANG: First, just a few very short comments about the talks today. I think they all illustrate one point, that the diseases which are being treated with steroids are a group of diseases which have prac-

tically unknown etiologies. What we are dealing with are results which are evaluated in terms of the clinical improvement rather than cure of the disease.

For myself I feel that several other things are important. They have been discussed here, and I won't go into them in detail. But I think that when you have a disease which needs to be treated, that the vigorousness of the approach is extremely important; that if a disease is worthwhile treating with steroids, with all their hazards, then the disease ought to be treated vigorously with the steroids.

Thyroid Suppression

I have one question. Dr. Bunim brought this out. I am going to ask Dr. Henneman to answer it. And that is in relation to the work with the suppression of the thyroid function, or at least some parameters of thyroid function, and whether there is any explanation. If I understand endocrinology as far as the pituitary is concerned, there is such a great specificity of the thyrotropic hormones, that it doesn't seem reasonable that the administration of, for instance, steroids or ACTH would have an effect on the TSH hormone. Is there some other explanation that is available, or is this just one of the unexplained clinical or laboratory findings?

DR. HENNEMAN: Usually you do not see any change in thyroid function in patients treated with corticoids. The decrease in ACTH output occurs regularly, measurably, every time and is dose-related. The suppression of thyroid function occurs irregularly and is usually fairly small in degree, and it has been rather hard to be very specific as to the mode of interference with thyroid function.

I don't know of any further data, other than what Dr. Bunim has presented, as to why this occurs. Clinically it does not seem to be of major importance, however.

DR. BUNIM: I should say I am glad the question came up because we are not clear in our own minds of the mechanism of thyroid suppression. There are several possibilities, and a recent review of the subject resulted in a conclusion that they still do not understand the mechanism of thyroid suppression by steroids.

Three Possibilities

One possibility is that it suppresses TSH, and that was sort of strengthened by the fact that upon administration of TSH to these patients who did have thyroid function suppression there was return, as you saw on the slide of the radioactive iron uptake.

Another factor that should be considered is the increased excretion of administered iron resulting from the administration of steroid therapy.

A third possibility is that there is a direct effect of the steroid on the thyroid gland, and that, too, has not yet been clarified, at least in man.

Mr. Chairman, if I may take the liberty of saying something which is not specifically in answer to the question—but takes issue on this point of preparing the patient for major surgery. We, at least in the field of arthritis, who have had extensive experience with steroids over ten years and have seen collectively thousands and thousands of patients who have to at times undergo emergency surgery, feel very strongly about this. I recognize that there may be a difference of opinion between the endocrinologists and the arthritis people because in sitting in at one of the meetings in Atlantic City of the Society of Clinical Investigation with the Federation I recall very distinctly the sort of collective conclusion on the part of the endocrinology section that, as Dr. Henneman said, it is not really necessary to prepare a patient for surgery with extra doses of steroid. The grim fact is that there have been deaths from surgery, or during surgery, or even during anesthesia before surgery was started in patients, who had received prolonged steroid therapy, and there was no

other explanation for those deaths than adrenal insufficiency.

Steroid Therapy Identification

We feel very definitely that these were preventible deaths. We are not alone in this because the Empire Rheumatism Council in England, a distinguished body of men who are critical of steroid therapy as a whole anyhow, nevertheless have now issued cards to every patient who is taking steroids, which he is to carry on his person, saying, "I am receiving steroid therapy. In case of emergency requiring either surgery or in case of severe trauma, please be sure to administer extra doses of steroid. Do not discontinue my steroid therapy."

There is evidence, histologically and physiologically, that prolonged steroid therapy very definitely, as Dr. Henneman said, suppresses adrenal corticoid function. That, together with the deaths, it seems to me would lead to the conclusion that there is no real objection whatever to a patient who had been receiving steroid therapy getting special preparation for the surgical emergency. We are not diverting treatment to any other condition. We are not having false confidence. We are not causing any serious side effects. We are not increasing the risk. There is nothing to be lost, it seems to me, and a great deal to be gained.

Now, I am willing to admit that a catastrophic adrenal insufficiency in such patients may not be common, but it is meager consolation to a family whose relative died post-operatively of adrenal insufficiency to say, "This rarely happens in general."

Therefore we at the Institute, and many other institutions, Mayo Clinic, and other places, have a definite schedule of preparation for surgery. Regardless of what steroid the patient is getting, he gets, in addition, cortisone acetate intramuscularly, one hundred milligrams, three times a day, for two days before surgery. This acts as a depot and will carry him over during the period when he is unable to take things by mouth. During the day of surgery we give about two hundred milligrams of cortef, which is soluble hydrocortisone; that is given intravenously during the operation, or two hours before the operation, and then for two days post-operatively we continue the same dosage of administration as the two days previous to operation, namely a hundred milligrams of cortisone three times a day.

It may be just good luck but we have not lost a single patient, and some of our patients have undergone very extensive surgery and were critically ill to begin with.

DR. TUMEN: May I say a word about that.

One of the objections that has been raised to steroid therapy in ulcerative colitis is the fact that some of these patients of course will come to colectomy, and this danger of steroids was emphasized in a paper from Yale a couple of years ago, in which it was indicated that some of the deaths following colectomy were the result of inadequate preparations of the patient, from a steroid standpoint, or ignoring the fact that steroids had been given six months or a year before.

Naturally the patients with colitis who come to colectomy are the sickest patients; they suffer from many depletions. Their risk is great. And certainly in those patients who have had any type of steroid therapy in the past, even though it is many, many months before, it is best to cover the patient.

I don't think there is any great difference between this point of view and the point of view that is expressed by Dr. Henneman because he indicated the need for preparation in patients who had had steroid dosage for any prolonged period of time. But certainly in patients with ulcerative colitis I should hesitate to let a patient go to surgery, go to colectomy, without adequate coverage of the type just described by Dr. Bunim.

DR. HENNEMAN: I would agree that most of you use large doses of corticoids when your patients are being operated on. However, since the occurrence of collapse is so rare in the corticoid-treated patients who are operated on who are not given any replacement therapy, I think the problem still needs study, and I wish that some group such as Dr. Bunim's, where the clinical care of the patient is ideal, would embark on a program of not replacing their patients but instead, measuring their blood corticoid response to surgery and in particular the blood corticoids of the patients who become hypotensive or who show other poor responses to surgery.

I think this problem needs further definition, and personally I am very skeptical of the fact that an occasional steroid treated patient unexpectedly going into shock proves that this is adrenal insufficiency. I have supervised the steroid replacement in a large number of these patients, and I have seen some of them who have received adequate steroids still develop marked hypotension if they have had procedures involving massive tissue damage.

Interference

I have also seen two instances where the program of corticoid replacement that Dr. Bunim recommends has apparently interfered with the response of the patient to infection, where there has been an abdominal infection secondary to the operation as a consequence of operating on an infected organ, where the post-operative course has been peculiar, the patient has been hypotensive, slightly fibril, after the corticoid in large doses was decreased the temperature has gone very high, there has been evidence of an uncontrolled, unlimited abdominal infection, presumably starting at the point of the original surgery.

So I think that this treatment is not entirely without any risks. I think that all of us are agreed at the present time that the conservative thing for people in practice to do is to treat these people as if they did have adrenal replacement. But my own feeling, and apparently this comes down to a matter of feeling because Dr. Bunim used the words "I feel very strongly" —so apparently this is not a matter of fact —since it is a matter largely of how the people feel, my feeling is that this will not turn out to be a very major problem.

The View Of The Ophthalmologist

DR. GORDON: I suppose as an ophthalmologist I should not rush in where doctors are arguing.

I think that we have got a difference of points of view here. I was a former general practitioner, and the general practitioner is interested, number one, in getting a very good result, and, number two, in his patient's comfort. I was in the ivory tower end, and the man in the ivory tower is interested in the cause and in statistics and not as much in comfort. He can learn a great deal about making a patient comfortable and about saving lives, perhaps, from the G.P. and the general surgeon. Now that I am in part time practice I am trying to combine the two points of view.

Now, I don't think that in the cases in which I am helping the patient—I don't know what this word "cure" means, by the way—a lot of my patients get better, and about fifteen per cent of my chronics never have to have steroids again—maybe that isn't a cure because I haven't attacked the pathogenic mechanism, but let's skip that. I don't think that I am giving the patient some steroids that he doesn't have. We are doing more than that. And I think that the patient who often has never had steroids and goes haywire after surgery or during an acute illness may not necessarily have a lack of steroids, and when we give that patient steroids and we get an improvement for which we can not account by chemical measurements of his blood or anything else, I don't think that this is a question that the patient has not had enough steroids; we have done something else; and because we can't account for it I don't think is a good reason for withholding it.

I have seen time after time and example after example where a patient was helped by steroids where the doctor or the surgeon had nothing else to give him. I was on a program with Dr. Coe from Chicago, who admittedly knew nothing about steroids but showed chart after chart where the internist had been called in on a patient who had been dying, had given steroids or ACTH and saved the patient's life.

I think it is justifiable even if we can't account for the rationale by any of our known chemical or other tests.

DR. WHITNEY: Thank you. Dr. LaMotte, do you have any unanswered problems from the standpoint of ophthalmology?

DR. LA MOTTE: I will make a comment or two. I think all ophthalmologists will agree with Dr. Gordon's statement that the use of steroids has revolutionized the treatment of eye disease. I would be inclined to qualify this or limit it largely to diseases of the uveal tract such as iritis and choroiditis, and diseases of the cornea and silera. Those of us who have been reading Dr. Gordon's papers and attending meetings where he has had exhibitis are familiar with his plea that when steroids are used they should be used, as he says, soon enough, often enough, and long enough.

Steroids For Superficial Infections

As far as a very commonly experienced lesion is concerned, which all general practitioners see, which Dr. Gordon commented on, namely, superficial infections, conjunctivitis, and so forth, I have always had some question in my mind, largely because of the expense to the patient, as to whether we were justified in using steroids when perhaps the disease is self-limiting and non-damaging, and when simple inexpensive chemotherapeutic agents locally would probably cure the patient. The local use of steroids probably contributes to the patient's comfort only as Dr. Gordon just said.

I would be inclined therefore, to urge the general practitioner not to use steroids on all red eyes which are obviously not anything but a conjunctivitis, and to avoid the routine use of steroid-antimicrobial combinations in such conditions. Maybe Dr. Gordon would not agree with that.

In connection with the use of steroids for uveitis of various types, Dr. Gordon suggested immediate treatment with systemic steroids because we can't find out what the cause is anyway. That has been one of the problems and that is the reason why steroids have revolutionized our therapy of that condition. There is at the present time a nationwide survey program sponsored by the U.S. Public Health Service and the American Academy of Ophthalmology and Otolaryngology in which those of us who have been cooperating are asked to take a patient and subject him to about 72 intracutaneous tests at one sitting, together with a lot of serological tests; certainly, the dozen or so we have done have come up with little or nothing in the the way of positive results, and we end up treating them with steroids anyway except in the few cases which might be presumably due to toxoplasmosis or tuberculosis.

I was wondering if Dr. Gordon agrees that we will never know the answers unless we keep looking for them; are such surveys a waste of time or not, and should we treat uveitis with steroids without thorough study of the whole patient?

I enjoyed your paper very much, Dr. Gordon.

DR. GORDON: Thank you. If I didn't say soon enough, often enough and long enough today, that is prima facie evidence of the fact that you have read at least one of my articles. I am glad someone besides my wife has read them.

The Patient, Comfort And The Cost

I agree, we have a lot of common ground here. I interned at Detroit Receiving Hospital during the depression and I found

any time I or any of the other interns looked askance at a patient obviously poverty-stricken, or something else happened that he didn't like, suddenly a rich relative showed up with a Cadillac and took him up to the local private hospital. And I think one of the mistakes I have made repeatedly is in losing patients because I have tried to save them money or a hospital bill, or something.

I know how you feel in this and I feel the same way, but I would not let the extra two or three dollars—it might not even be that—stand in my way. At one meeting a doctor said to me, after seeing one of these red eyes, that this patient would get better anyway within three weeks, why give steroids? I said I would like him to be comfortable for those three weeks. And having had a very bad acute conjunctivitis myself, which put me out of work for two weeks, I am all in favor of it.

Recently we had a Pseudomonas infection of the cornea which did not respond to polymyxin and over the weekend one of the residents put some steroids in his eye and the eye promptly cleared up.

I think this laboratory survey of uveitis is useless. The paper I gave about a month ago, which one of the journals of ophthalmology has accepted, said this: We are getting nowhere with our present survey in uveitis and the genral practitioner in ophthalmology should not bother too much with this; he should leave it for the lab men to devise new tests. I think the old tests have not succeeded.

We have cooperated in this study which was instigated by one man. One of his leading graduates, by the way, who is a professor at one of the big medical schools, has flatly refused to cooperate in this survey because he knows it is a waste of time. We know it is at our place but we have tried to be courteous and cooperate. We have gotten absolutely nowhere on this survey. And I have had internist after internist come up to me and say, "I am in charge of uveitis surveys in my hospital and I think it is a waste of time and when are you fellows going to stop this?" And I have to agree with this. I hate to take away business from the mouths of starving internists but I don't think we are getting anywhere with present methods and it is up to the lab men, the men really interested in lab work in uveitis, to pursue this approach.

As far as Daraprim and sulfonamides in toxoplasmosis are concerned I don't think daraprim itself is a specific. Most of the papers which are reporting a great deal of success in the treatment of toxoplasmosis with daraprim and sulfonamides have used steroids concomitantly and just forget to mention it in the summary, and nobody ever reads the case reports. But it is in there.

As far as tuberculosis is concerned, I don't think tuberculosis is important in human ocular pathology any more. If there is anything to point to the existence of it, I think you ought to cover it with anti-tubercular therapy as the other men have mentioned. I think that we see eye to eye on this.

DR. WHITNEY: In the five remaining minutes I would like to welcome questions from the floor.

DR. HALL: Dr. Bunim, about two years ago in Boston I heard you speak on this danger of polyarteritis developing in steroid patients. I would like him to enlarge a little bit on his subsequent experience with that. I would like to know if it develops also in patients on gold, if it develops in patients with rheumatoid arthritis on aspirin alone, and what is the mortality in this. He indicated then that all we would do would be to slow down on steroids. Is there any better treatment now?

DR. BUNIM: This is really a very difficult problem, as it will become apparent to you from simple statements that, first, on very careful studies made on patients with rheumatoid arthritis before the steroid era we found that random biopsy of the grastroc-

nemius muscle showed a vasculitis in patients with rheumatoid arthritis. It is true that the vasculitis was mild; it consisted of very definite inflammatory cellular infiltration. There was no necrosis. These are vascular-free symptom patients with rheumatoid arthritis.

But from that study we have concluded that vasculitis is an integral part of the pathological picture of rheumatoid arthritis. This has since been confirmed by a number of observers, most recently by Dr. Cruckshank in Scotland, who found on autopsy of patients with rheumatoid arthritis who had never received steroid therapy, 19 per cent had vasculitis, including polyarteritis nodosa in some of this 19 per cent.

So that we know that without steroid therapy these lesions can occur. The severity ranges from mild cellular infiltration to necrosis of the wall in the kind of picture you saw on the screen.

Now, as a control, patients with ankylosing spondelitis, in autopsy by Dr. Cruckshank, the incidence of vasculitis is only one per cent. Nevertheless, although we know that this can occur, although we haven't collected valid statistics, there is an unequivocal impression among people in this field that the incidence of vasculitis in patients treated with steroids is constantly increasing and has reached in some areas rather alarming proportions. But, as I said before, we don't know whether it is the administration of the steroid which causes an exacerbation of an already existing vasculitis or whether we are dealing with the more severely ill patients with active disease, and when we taper the steroid the disease exacerbates, and what we are seeing is an exacerbation of the disease because it is not controlled rather than something directly resulting from the administration of the steroid.

Now, how to deal with this problem clinically is again a rather difficult question to answer. The only thing I can say is that we deal with these patients on an individual basis. For example, we know that polyarteritis nodosa of the classical type, such as described by Meyer and Kussmal in the late part of the nineteenth century, that classical type of polyarteritis nodosa, unrelated to over hypersensitive and unrelated to rheumatoid arthritis, that type that responds in some cases, not uniformly but in some cases very dramatically to steroid administration, and, as a matter of fact, this is about the only measure that is being used.

Therefore it would seem on logical grounds if this is the treatment for unprovoked or idiopathic polyarteritis nodosa, then certainly when the patient develops this as a complication of rheumatoid arthritis, this ought to be good treatment. Therefore in many instances we found that when we increase the dosage of steroid in such patients who had developed polyarteritis nodosa during the course of rheumatoid arthritis under previous therapy that such patients improve.

I have recently seen one such patient at Johns Hopkins who did very well when the dose was increased to 60 milligrams of Prednisone daily. On the other hand, there is the risk that it might be pushed the other way, and the only thing you can do is trial and error and watch the patient very carefully and see how he responds to it. Sometimes our initial attempt is to reduce steroid therapy by very careful tapering off in such patients, and that, too, has worked.

We do not have the answer. We do not understand the pathogenesis of it, and the only course we can take is one of expectant individualized therapy. In some instances we are forced to increase the dosage and we get improvement. In other instances we attempt to taper and discontinue the drug.

DR. HALL: Is there any advantage in changing from the corticoid steroid to ACTH?

DR. BUNIM: No. I don't think so.

President's Page

OUR UNIVERSITY

From the report of President John A. Perkins, University of Delaware, 1959-60, one may glean the following nuggets:

There were 5,820 individuals enrolled in our University in the autumn of 1960. Approximately half of the college-bound students from Delaware's preparatory schools go to institutions outside of the state. The yen of the college freshman to get a distance from home is shown in the fact that the number of qualified applicants from beyond the borders of Delaware could have filled the freshman class at the University of Delaware this year "twice over." One thousand eighty-seven at the U. of D. are graduate students.

Our University has been developed largely from the private resources of donors who did not intend to create a highly provincial educational institution. Its cosmopolitan student body and exceptionally competent faculty has created a remarkably effective training ground for our youth.

A commendable emphasis in the School of Education is its concentration on the training of able teachers of mathematics. A fine dividend may be anticipated in the better preparation in this area of students applying for college admission in the future. Support in this emphasis was given by the 120th Delaware General Assembly through its Joint Finance Committee, Walter J. Hoey, Chairman, in the appropriation of funds to build a new mathematics and physics building.

From the examination of our need for additional medical graduates in the nation, President Perkins points out the problems in creating new medical schools, keeps an open mind on the subject and observes that "the desperate need for medical schools in the nation as a whole and the likelihood of our State as a fitting place to meet this need require thorough and objective examination." The writer would add that this need for Delaware and the nation to be feasible calls for significant financial support from private sources of capital. Medical education should be done well, and to do so is costly. Only a small part properly can be contributed by taxes from our citizens. Existing responsibilities and programs supported by the State have justifiable priority. A more logical contribution by our University in the near future may be the preparation, through its graduate school, of teachers qualified to fill vacancies now existing in preclinical sciences in presently established medical schools.

Samuel C. McGee

Editorials

CLINICAL ELECTROCARDIOGRAPHY

Several different aspects of electrocardiographic interpretation have recently been subjected to analysis and the results have been reported. At first glance some of these studies appear to cast doubt upon the objectivity of the electrocardiogram as a clinical tool but closer study shows that valid criticisms have been made and, to some extent, ideas for betterment of interpretation have been advanced.

Davies,[1] in 1958 and Segall,[2] in 1960, each took 100 electrocardiograms (ECGs) and had them interpreted by 10 and 20 different observers respectively. Furthermore, each observer was shown the same tracing on more than one occasion in an attempt to determine consistency of observation of a single observer. The first series included 9 cardiologists and one general practitioner; the second consisted of a smaller number of men trained in ECG interpretation and a larger number of untrained personnel. Both groups showed (1) a lack of agreement between trained personnel, (2) a greater lack of agreement between trained vs. untrained personnel and between untrained vs. untrained personnel, (3) and finally a lack of agreement when either a trained or untrained person re-examined the same tracing after a period of several weeks. In this latter divergence, it was found that the untrained personnel varied more widely than the trained.

All of these results are logical and could have been predicted.

Epstein and five other experts[3] recently reported their experience in the interpretation of 451 ECGs taken upon young soldiers during a nutrition survey in Spain. Despite the homogenous examiner element, there remained a considerable amount of variation, particularly in the region of "borderline" tracings. This study differs significantly from the first two in that there was a preponderance of normal tracings. Furthermore, it is unfortunate that the authors did not see fit to give a description of the exact "borderline" abnormalities where most of the disagreement occurred.

Epstein and his colleagues believe that much of the difficulty is due to an attempt to force tracings into a narrow diagnostic category. They believe that to correct this error, emphasis should be placed on the objective description of the tracing.

We heartily agree that ECGs (also x-rays and similar procedures) should be *read* in an objective manner, mention being made of changes without speculation as to their cause. We will never agree, however, that the report should stop at this point. The reading should be followed by an *interpretation* and in this section the reporter should be encouraged to express his opinion. The wise man will interpret a tracing only after correlating it with the clinical data. The report should have a dividing line to show clearly where the reading ends and the interpretation begins.

The ECG is an objective test. It is possible to keep the report objective. One must not confuse objectivity with infallibility and, more important, one should not confuse a criticism of the procedure with a criticism of those who use that procedure.

The ECG is a good, objective procedure By clearly dividing the report into a *reading* and an *interpretation*, the value of this procedure can be preserved.

REFERENCES

1. Davies, L. G.: Observer variation in reports on electrocardiograms, Brit. Heart J. 20:153, 1958.
2. Segall, H. N.: Electrocardiogram and its interpretation: Study of reports by 20 physicians on set of 100 electrocardiograms, Canad. Med. Ass. J. 82:2, 1960.
3. Epstein, F. H., Doyle, J. T., Pollack, A. A., Pollack, H., Robb, G. P., and Simonson, E.: Observer interpretation of electrocardiograms: Suggestions for objective interpretations, J. A. M. A. 175:847 (Mar. 11), 1961.

New Members

Robert T. Beattie, M.D., is a Texan by birth. He received his medical training at McGill University and obtained his Delaware license in 1957. Dr. Beattie is living in one of those charming New Castle houses, circa 1730, and his remodeling ideas will constitute an endless hobby. A two year old son and a practically new daughter rule the household. Specialty: Industrial Medicine. Office: 212 Delaware St., New Castle.

Milton S. Wahl, M.D., is a natvie Wilmingtonian. All his preparatory schooling was in Delaware, his medical education at Indiana University School of Medicine. He received his Delaware license in 1954. Specialty: Otolaryngology. Dr. Wahl likes all country sports, such as fishing and hunting—or just taking a walk—with golf as a runner-up. Office: Professional Building, Wilmington.

Gerhard Hartenauer, M.D., George-August University Medical School, Germany, came to this country in 1953, sponsored by the Reed Program of the Ventnor Foundation. After a year's internship in the Atlantic City Hospital, Dr. Hartenauer returned to Germany and served one and a half years in the American Air Force Hospital, Frankfort. A fellowship in cardiology brought him back to start special training in internal medicine at the Delaware Hospital. Office: 1501 N. Broom St., Wilmington.

James Strong, M.D., a native Texan, is a graduate of Baylor University School of Medicine. He left his post as assistant director of Public Health in Dallas, to come to Wilmington as Health Commissioner. Dr. Strong enjoys spectator sports such as baseball and football, and photography is his hobby. The Strongs have four daughters. As a family they enjoy music on their Hi-Fi or at concerts. Office: 1213 Walnut St., Wilmington.

In Brief

The Cheese Stands Alone

Milk and milk products such as cheese may provoke ulcerative colitis, according to an article in the British Medical Journal by S. C. Truelove, M.D., University of Oxford. Though food allergy as an important cause of this condition is not generally accepted, Dr. Truelove found that in treating a group of patients with ulcerative colitis, the removal of milk and cheese from their diets was followed by a marked improvement in their condition. Butter and cooked cheese were not found to be causitive factors.

High Price Of Vaccine

Dr. Albert Sabin, who developed the oral polio vaccine, criticized President Kennedy's request to Congress for an appropriation of one million dollars to purchase supplies of live virus vaccine. Dr. Sabin's remark, "They picked their price right out of the air," referred to an overestimation, in his opinion, of the actual price of the vaccine when it reaches production.

Delaware Hospitals Accredited

Eleven Delaware hospitals have been accredited by the Joint Commission on Accreditation of Hospitals. They include the Alfred I. duPont Institute, Emily P. Bissell, The Memorial, St. Francis and Wilmington General Hospitals, Wilmington; Kent General, Dover; Delaware State, Farnhurst; Beebe Hospital, Lewes; Milford, Memorial; and Nanticoke Memorial, Seaford.

Medical Disaster Exercise

A health mobilization emergency hospital training program will be held in the Dover Armory on May 12, 1961. A one-day training exercise, the Institute is offered so that Delaware medical and hospital personnel may learn the assembly and operation of the 200-bed Civil Defense Emergency Hospital (CDEH). A team of local people will erect and operate the hospital for a series of mock casualties from the Dover area.

In the event of a serious natural or military disaster, the role of the emergency hospital is vital. Its efficiency depends directly on there being trained personnel available to operate it. The participation of doctors, dentists, nurses, technicians and all health workers are needed in the Health Mobilization Program.

The exercise is co-sponsored by a number of organizations, including the Medical Society of Delaware, and is under the direction of Mr. W. C. Anderson, president of the Association of Delaware Hospitals and Mr. Eugene Trivits, Delaware's representative of the United States Public Health Service's Division of Health Mobilization.

A team of Kent County physicians comprised of Drs. Lawrence M. Baker, James B. McClements, John J. Lazzeri, Eugene R. McNinch, Rhoslyn J. Bishoff, James R. McNinch, and E. Harold Mercer will erect and staff the hospital during the exercise. Other Delaware doctors are invited to come, watch, and learn.

Personal Glimpses

Albert J. Wildberger, M.D., was speaker at the Georgetown Kiwanis Club; topic *Medicine in Our Community* . . . James A. Flaherty, M.D., was a member of the Ursuline Academy Association's forum on *The Effects and What Can be Done About Pornographic Literature* . . . Henry V. P. Wilson, M.D., Dover, is one of the Trustees appointed to the University of Delaware . . . Douglas M. Gay, M.D., participated in a demonstration at the opening of the new electrical laboratory at Wilmington General Hospital . . . A. R. Shands, Jr., M.D., and F. A. Freyhan, M.D., addressed the Scientific Assembly of the Virginia Academy of General Practice; Dr. Shands' topic was *Orthopedic Aspects* and Dr. Freyhan's was *The Use and Misuse of Tranquilizers* . . . Dr. Freyhan has a dual appointment with the National Institute of Mental Health and St. Elizabeth's Hospital, Washington, D.C., as Director of Clinical Studies; in addition to this he has been appointed clinical professor at George Washington University . . . Arthur J. Heather, M.D., will participate in a program of the American Congress of Physical Medicine and Rehabilitation to be held in April; topic *Orthotic Devices for Hand Paralysis* . . . Carl Glassman, M.D., and Howard Wilk, M.D., have been appointed captains of the special gifts division for the Jewish Federation of Delaware's 1961 Fund Drive . . . Charles K. Bush, M.D., was a speaker at a weekly luncheon of the Wilmington Quota Club . . . Norman L. Cannon, M.D., participated in a program *Opportunities in Paramedical Professions* held for upper school students at Friends School . . . Harry G. Neese, Jr., M.D., appointed to town Board of Health, Wyoming, Delaware . . .

Maryland State Meeting

April 26-28 are the dates set for the 163rd Annual Meeting of the Medical and Chirurgical Faculty of the State of Maryland, to be held at the Alcazar, Cathedral & Madison Strs., Baltimore. Delaware physicians are invited.

New Concepts In Exercise . . .

Strenuous housework burns up 6.6 calories per minute, compared to a mere 4 to 5 calories a minute for gardening, golfing, or walking briskly, according to Herman K. Hellerstein, M.D., Cleveland cardiologist.

Arthritis . . .

Arthritis is robbing the cradle, says the National Foundation of rheumatoid arthritis. Parents are cautioned not to dismiss aching in children's necks, knees or elbows as "growing pains."

Heart Status . . .

Heart attacks strike lower salaried men more frequently than high income executives, according to a study made by Drs. C. A. D'Alonzo and Sidney Pell, Wilmington.

Space Health . . .

Kidney stones caused by stress deprivation may be the penalty for space trips. Astronauts may be confronted by the same problem faced by patients confined to bed for extended periods.

Blood Vessels . . .

Synthetic grafts made of Teflon to replace damaged or diseased blood vessels are now being studied and tested at the University of Pennsylvania under funds granted by the Delaware Heart Association.

Auxiliary Affairs

● An account of a vacation that was different, fresh, and remote from the daily routine, is given by an Auxiliary member who wishes to remain anonymous.

We discovered an unusual vacation recently, which other Auxiliary members might enjoy. We flew to Nassau by British Overseas Airways from New York, and then flew by Bahama Airways to the island of Abaco, the northernmost of the Bahama Islands. There we landed at Marsh Harbour Airport, which operated during daytime only and then only when a plane was due. Arrangements had been made to charter a schooner for four people, the "Caribe," a 68 ft., 3½ ft. draft, Alden-designed boat. We planned to spend about 11 days aboard, cruising among the cays. We were greeted by the young captain, H. Lee Brooks, and his wife, Jo, who were Georgia Tech graduates (engineering and home economics), and who had decided this was the life for them. He sported a red beatnik-type beard, which aroused a few doubts at first.

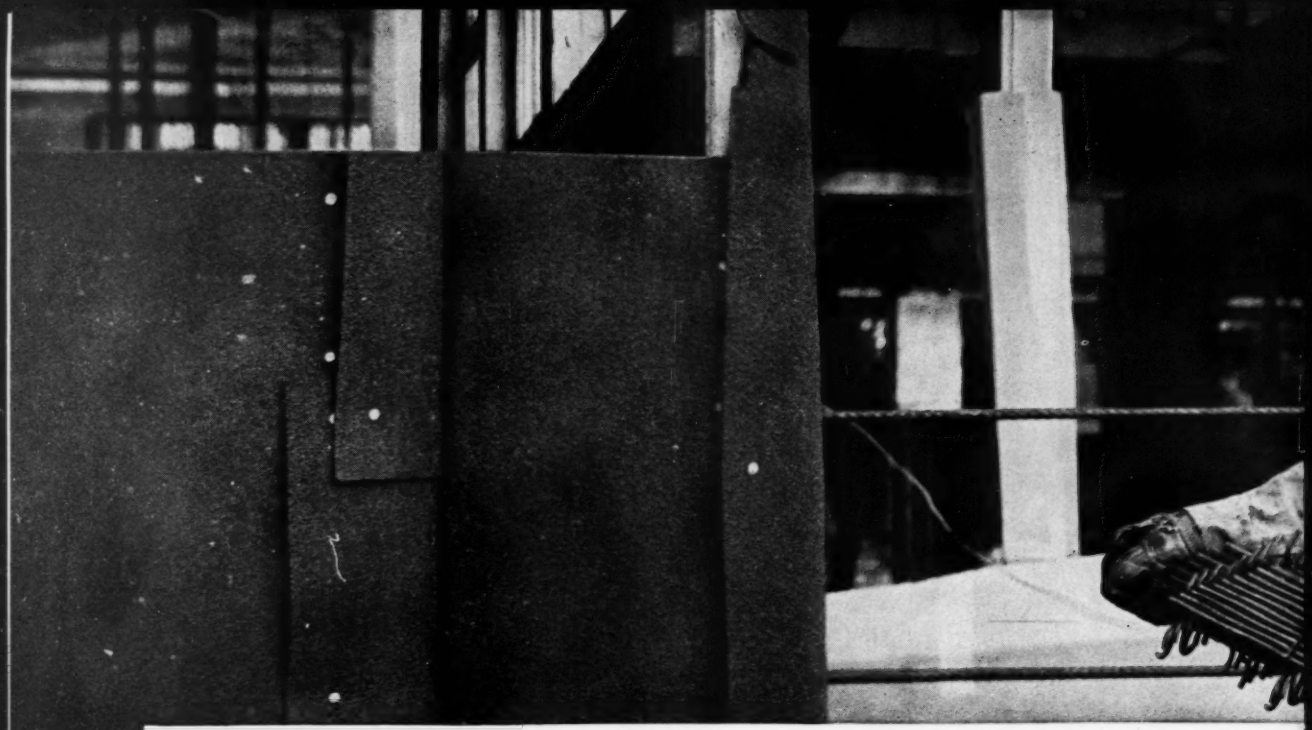
The first problem was to get aboard via dinghy. Dresses are not recommended for this; even when properly attired, it was always a question whether you would fall in. Once aboard we found everything provided for according to our tastes. They had written beforehand for our food and beverage preferences. It didn't take long to know our captain was tops and our cook superb.

The schooner boasted two staterooms plus captain's quarters, two heads, wardroom (dining room) and galley. There was ample deck space for sunbathing and walking. Most of the time aboard was spent fishing or swimming. The captain and his wife were graduate skin divers and had all the necessary equipment aboard and a willingness to teach. You had to watch for barracuda when swimming and skin diving, but the water is so clear you can see right to the bottom. We enjoyed seeing all the coral formations, starfish and other fish. And we had several meals from the sea, including lobster tails from crayfish.

Cruising was done by daylight only because there were no channel markers to sail by. Navigating is done by color of water and the skipper's experience. The Abaco Islands are protected by numerous small cays, which provide about 100 miles of good protected sailing waters. We very seldom used the motor; used sails almost entirely.

A highlight of the trip was landing at Green Turtle Cay to find another Delawarean operating a small resort. It was good to be on land again after six days aboard. The food was delicious after on honest-to-goodness shower. We found that everyone on these cays has to have his own power plant; and water is a problem for the rain must be caught in large tanks for your use.

After several more leisurely days of cruising, we returned to Abaco, unloaded our bags to return to Nassau. We heartily recommend this for a complete vacation. For information you may write to Capt. H. Lee Brooks, Hudson Schooner Sailings, Inc., P.O. Box 44, New York 63, N.Y.



Put your low-back patient back on the payroll

Soma's prompt relief of pain and stiffness can get your low-back patients back to work in days instead of weeks

Soma is unique because it combines the properties of an effective muscle relaxant and an independent analgesic in *a single drug.* Unlike most other muscle relaxants, which can only relax muscle tension, Soma attacks both phases of the pain-spasm cycle at the same time.

Thus with Soma, you can break up both pain and spasm fast, effectively . . . help give your patient the two things he wants most: relief from pain and rapid return to full activity.

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only with higher dosages. Soma is available in 350 mg. tablets. Usual dosage is 1 tablet q.i.d.

The muscle relaxant with an independent pain-relieving action

SOMA®

(carisoprodol, Wallace)

Wallace Laboratories, Cranbury, New Jersey

How you can help save your patients a month's pay

Kestler reports in J.A.M.A. (April 30, 1960) that conventionally treated low-back syndrome patients required an average of 41 days for full recovery (range: 3 to 90 days). The addition of Soma therapy in this comparative investigation reduced the average to 11.5 days (range: 2 to 21 days). With Soma, patients averaged full recovery 30 days sooner.

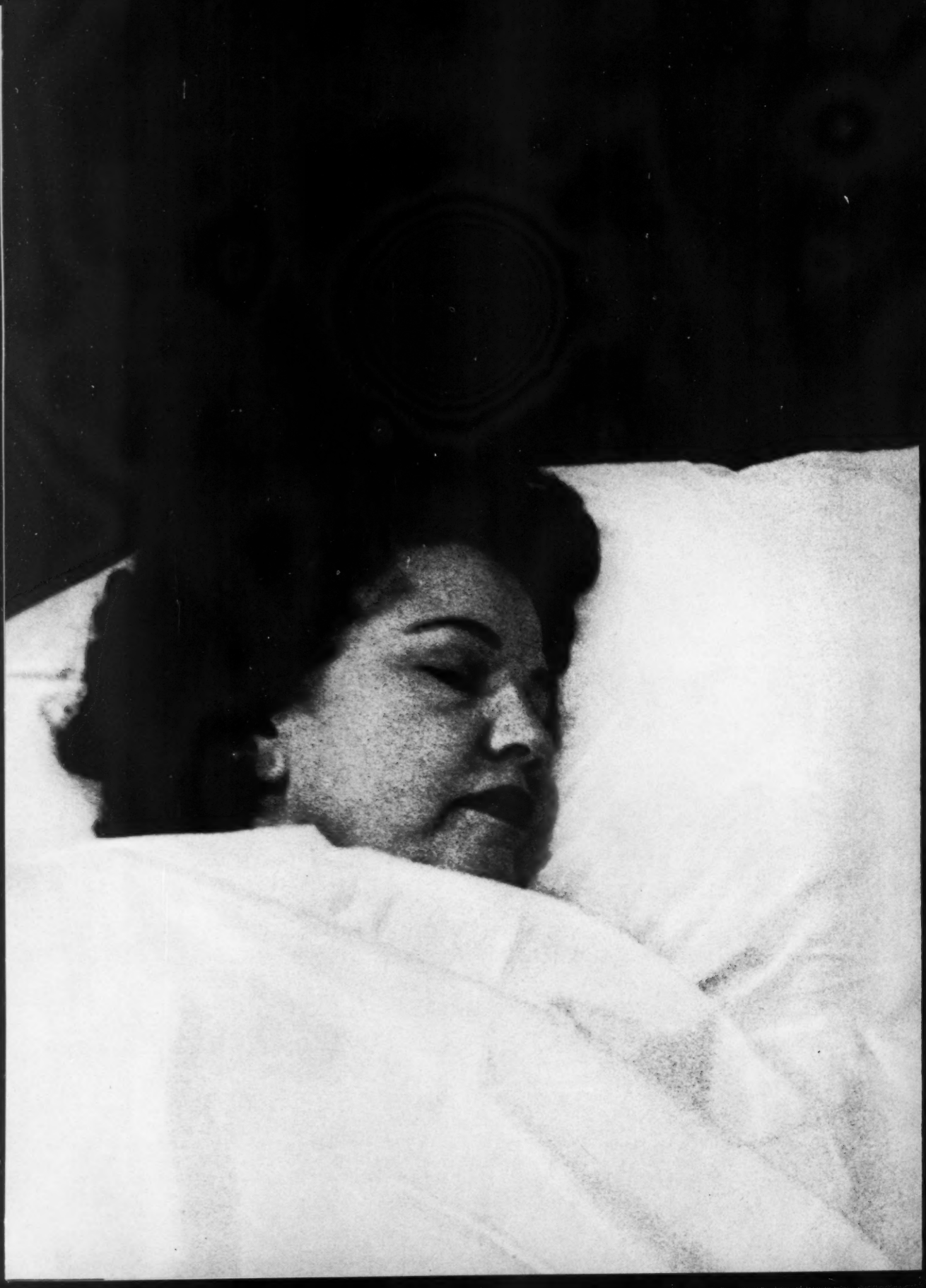
Why Homer Jackson's work is important to you...

Talking on the radio-telephone is Homer "Bud" Jackson, both a scientist and a hard-working buyer for a company processing Florida oranges into frozen juice concentrate.

He has just made a decision that's important to you. He has analyzed some sample oranges from the grove in the background and found that they have the optimal amount of sugar, of acid, and are of the proper texture. (Testing for vitamin C comes later.) Homer Jackson knows that these oranges are of a quality to meet the exacting regulations required by the Florida Citrus Commission.

These standards for quality in citrus products are the highest in the world. This is important to you and your patients because juice made from the best oranges will be nutritionally best for your patients. It will contain abundant amounts of vitamin C and rich, natural fruit sugars.

It's good nutrition to encourage people to drink orange juice. It makes good sense to persuade them to drink orange juice that you *know* tastes good, has the right sugar-acid ratio, and is packed full of nutritionally important vitamin C.



in sulfa therapy...

RELEASE YOUR PATIENT FROM Q.I.D. DOSAGE

just one tablet of Midicel provides continuous, effective blood levels for 24 hours

Because many patients need take only 1 tablet daily, therapy with MIDICEL is convenient and economical. It is also advantageous since the possibility of omitted doses is reduced. Rapidly absorbed and slowly excreted, MIDICEL assures dependable bacteriostatic action in urinary tract infections, certain respiratory infections, bacillary dysenteries, as well as surgical and soft-tissue infections caused by sulfonamide-sensitive organisms. And with MIDICEL, there is little likelihood of crystalluria because of its high solubility and low dosage.

MIDICEL (sulfamethoxypyridazine, Parke-Davis), 3-sulfanilamido-6-methoxypyridazine. Tablets of 0.5 Gm.; Suspension, each cc. containing 50 mg. of sulfamethoxypyridazine as the N'-acetyl derivative. *Indications:* Gram-negative and gram-positive infections such as urinary tract, respiratory, and soft-tissue infections and bacillary dysenteries. *Dosage:* Orally once a day until asymptomatic for 48 to 72 hours. Adults:—1 Gm. initially, followed by 0.5 Gm. daily thereafter or 1 Gm. every other day. In severe infections, not to exceed 2 Gm. the first day, then 0.5 to 1.5 Gm. daily according to weight of patient and severity of infection. Children:—30 mg. per Kg. the first day, then 15 mg. per Kg. daily. In severe infections, up to 50 mg. per Kg. initially, then 25 mg. per Kg. daily. Total dose in children, however, should not exceed lower dosage limits for adults. *Precautions:* Continue daily doses higher than 0.5 Gm. no longer than three to five days without checking for blood levels above therapeutic range. Maintain adequate fluid intake during therapy and for 48 to 72 hours afterward. Until further definitive information is available, MIDICEL, in common with all sulfonamides, is contraindicated in the premature and newborn infant. Contraindicated in patients with a history of sulfa sensitivity. MIDICEL is not recommended for meningococcal infections. *Side Effects:* Anorexia and lassitude may occur as may reactions such as drug fever, rash, and headache, all of which are indications for discontinuing the drug. Leukopenia has been reported. Periodic blood counts are advised. Patients with impaired renal function should be followed closely since excessive accumulation may occur. *Available:* Quarter-scored tablets of 0.5 Gm., bottles of 24, 100, and 1,000.

60181

Midicel

(sulfamethoxypyridazine, Parke-Davis)

and for children...Midicel Acetyl Suspension (N¹ acetyl sulfamethoxypyridazine, Parke-Davis) • delicious butterscotch flavor • only one dose a day

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

For the build-up in convalescence

ANNOUNCING

FILMTAB® SURBEX-T™

Therapeutic dosage of B-Complex plus 500 mg. of Vitamin C

Unsurpassed stability. As coatings are applied without water, deterioration due to moisture is virtually eliminated. Stability is enhanced; potency is protected. **Easier, more pleasant to take.** SURBEX-T tablets are up to 30% smaller; have a pleasant taste; and are non-caloric. Vitamin odor and aftertaste are eliminated.

Each Filmtab SURBEX-T represents:

Thiamine Mononitrate (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Nicotinamide	100 mg.
Pyridoxine Hydrochloride	5 mg.
Cobalamin (Vitamin B_{12})	4 mcg.
Calcium Pantothenate (as calcium pantothenate racemic)	20 mg.
Ascorbic Acid (as sodium ascorbate)	500 mg.
Desiccated Liver, N. F.	75 mg.
Liver Fraction 2, N. F.	75 mg.

Supplied in bottles of 100 and 1000

VITAMINS BY ABBOTT

Filmtab coatings protect this full range of Abbott nutritional supplements:

SUR-BEX® WITH C. Smaller dosages of the essential B-Complex and C. Table bottles of 60. Also in bottles of 100, 500 and 1000.

DAYTEENS™ To help insure optimal nutrition in growing teenagers. Table bottles of 100, bottles of 250, 1000.

Potent maintenance formulas —ideal for those who are "nutritionally run-down"

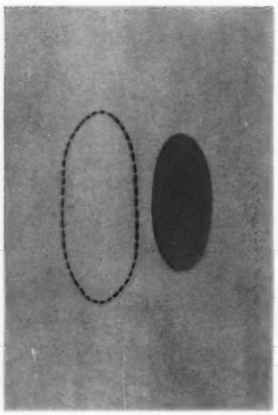
DAYALETS® Table bottles of 100. Bottles of 50, 250, 1000.

DAYALETS-M® Apothecary bottles of 100 and 250. Also in bottles of 1000.

Therapeutic formulas for more severe deficiencies—illness, infection, etc.

OPTILETS® & OPTILETS-M® Table bottles of 30 and 100. Bottles of 1000.

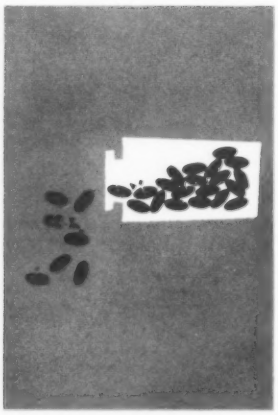
Filmtab® Coating Advantages in a Nutshell



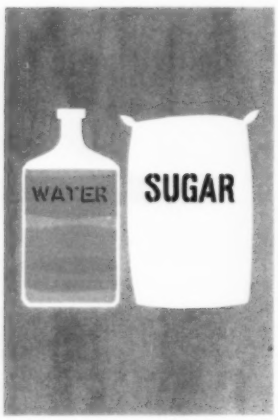
Tablets are easier to swallow, up to 30% smaller.

Vitamin after-taste and odor are eliminated.

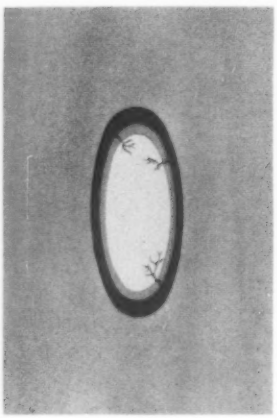
Tablets are pleasant tasting, non-caloric, come in a rainbow of cheerful colors.



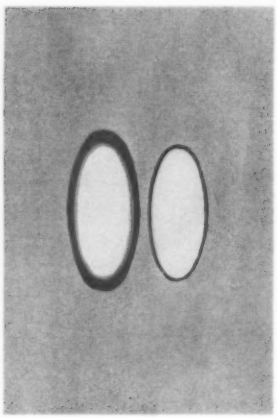
Breakage and cracking are less likely. (Sugar coatings are crystalline, and more brittle.)



In contrast with sugar coatings, no water is used in manufacture.



This eliminates the need of protective subseals, and chances of moisture seepage through imperfections.



Absorption is speeded as sugar's bulk and subseals are eliminated.

Vitamins are readily available at proximal receptor sites.

NET RESULT: Potency is assured for a longer time. The patient gets what he pays for—and what you prescribe.

ABBOTT

for more satisfactory relief of anxiety-aggravated pain

PHENAPHEN®

- More satisfactory than "the usual analgesic compounds" for relieving pain and anxiety.[1]
- More effective than a standard A.P.C. preparation for relief of moderate to severe pain.[2]

Each PHENAPHEN *capsule contains:*

Acetylsalicylic acid (2½ gr.)	162 mg.
Phenacetin (3 gr.)	194 mg.
Phenobarbital (¼ gr.)	16.2 mg.
Hyoscyamine sulfate	0.031 mg.

Also available:

PHENAPHEN with CODEINE PHOSPHATE
¼ GR. (16.2 mg.) Phenaphen No. 2

PHENAPHEN with CODEINE PHOSPHATE
½ GR. (32.4 mg.) Phenaphen No. 3

PHENAPHEN with CODEINE PHOSPHATE
1 GR. (64.8 mg.) Phenaphen No. 4

Bottles of 100 and 500 capsules.

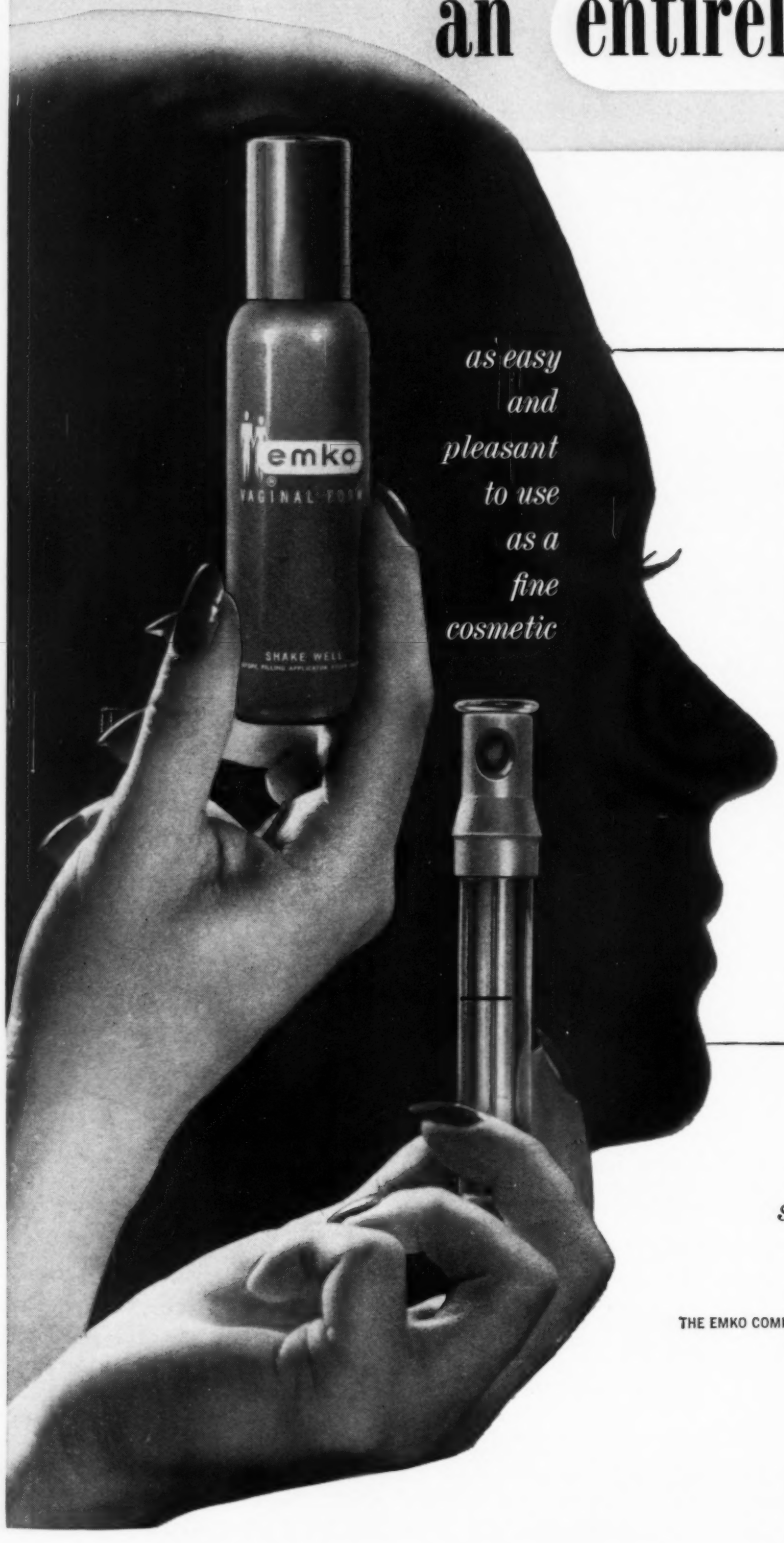
1. Meyers, G. B.: Ind. Med. & Surg. 26:3, 1957. 2. Murray, R. J.: N. Y. St. J. Med. 53:1867, 1953.

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

Making today's medicines with integrity... seeking tomorrow's with persistence.

Robins

an entirely different



as easy and pleasant to use as a fine cosmetic

EMKO BACKGROUND

Joseph Sunnen, an inventor and industrialist widely known for his philanthropic work, became concerned about the serious economic problems caused by the high birth rate in Puerto Rico. There was an obvious need in that country for a contraceptive more acceptable to the people than the standard creams and jellies.

He suggested combining a proven spermicidal agent with an aerosol foam as a basic carrier. The resulting product, Emko Vaginal Foam, proved simple to use, free of greasiness, and economical.

For the past three years, Emko has been made available in Puerto Rico through the Family Planning Association and the Government Department of Health. Approximately 35,000 families are now using it.

The success of Emko Vaginal Foam in Puerto Rico, and the support it has received from the many people who have visited there, led to the decision to make Emko available to doctors and their patients in the United States.

NOW YOU CAN
PUT YOUR PATIENT'S MIND
AT EASE... WITH EMKO

stocked by local drug stores

THE EMKO COMPANY • 7912 MANCHESTER AVE. • ST. LOUIS 17, MO.

approach to birth control

emko®
VAGINAL FOAM*

...using principles never before applied to contraceptives

• THE FIRST AEROSOL FOAM!

The volume of the material is expanded ten times to create A BLOCK OF FOAM.

• THIS BLOCK SEALS THE CERVICAL OS.

Only a FOAM can successfully serve this diaphragm-like function . . . without interfering with normal intercourse or reducing sensory contact.

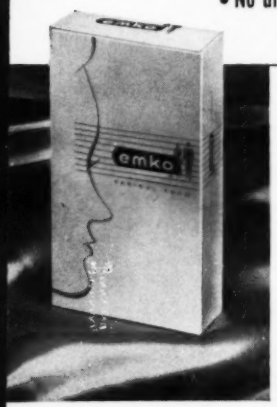
• A HIGHLY EFFECTIVE PROVEN SPERMICIDE

EMKO Vaginal Foam contains the widely used and thoroughly proven spermicide Nonyl phenoxy polyoxyethylene enthanol 8.0% and Benzethonium Chloride 0.2%.

The total surface area of each bubble of foam contains this highly effective spermicidal combination. As the sperm attempts to penetrate the block of foam, its zig-zag course exposes it constantly to this very large contact area created by the bubbles.

Thus, Emko Vaginal Foam assures maximum spermicidal exposure . . . with a minimum weight of material.

• No douching . . . it vanishes after use **• Absolutely no greasiness or "after-mess"**
• No diaphragm . . . the foam does the blocking **• No irritation for husband or wife**



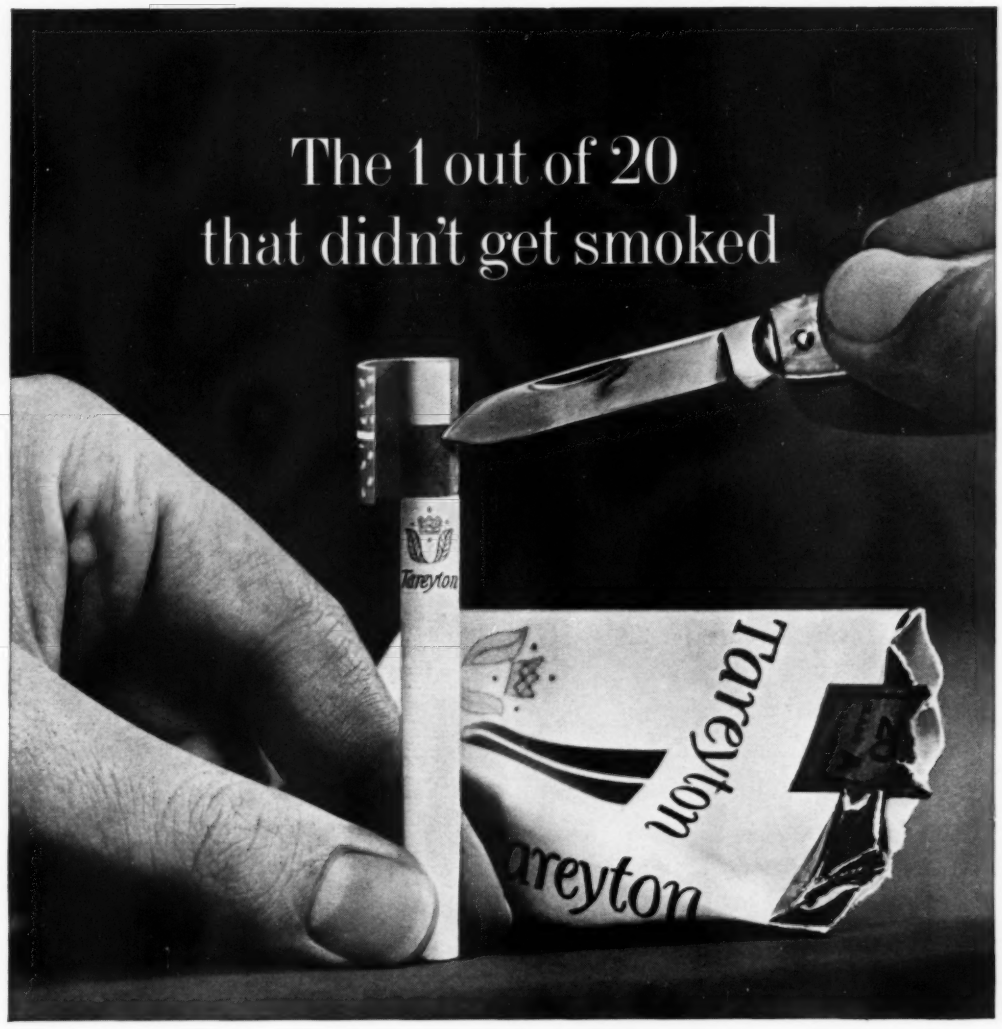
MARGARET SANGER RESEARCH BUREAU/**INTERIM REPORT**

In the Contraception Service of the Margaret Sanger Research Bureau, through October 31, 1960, Emko had been used from one to 22 months by 362 patients, with a total of 12 unplanned pregnancies. Seven of the pregnant patients admitted irregularity in the use of Emko.

Two planned pregnancies had also occurred after stopping the use of Emko.

A. J. SOBRERO, M.D. *Research Director*

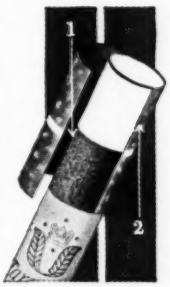
*PAT. NO. 2,943,979, OTHER PATS. PEND.



There's a lot of satisfaction in pointing out something good to a friend. That's why it sometimes happens that one cigarette out of a pack of Dual Filter Tareytons never does get smoked.

People open it to show its remarkable Dual Filter containing Activated Charcoal. They may not know why it works so well, but they do know this: it brings out the *best* taste of the *best* tobaccos. Yes, Tareyton delivers the flavor . . . and the Dual Filter does it!

Try a pack of Dual Filter Tareyton. We believe the extra pleasure they bring will soon have you passing the good word to your friends.



Tareyton delivers the flavor . . .
DUAL FILTER DOES IT!

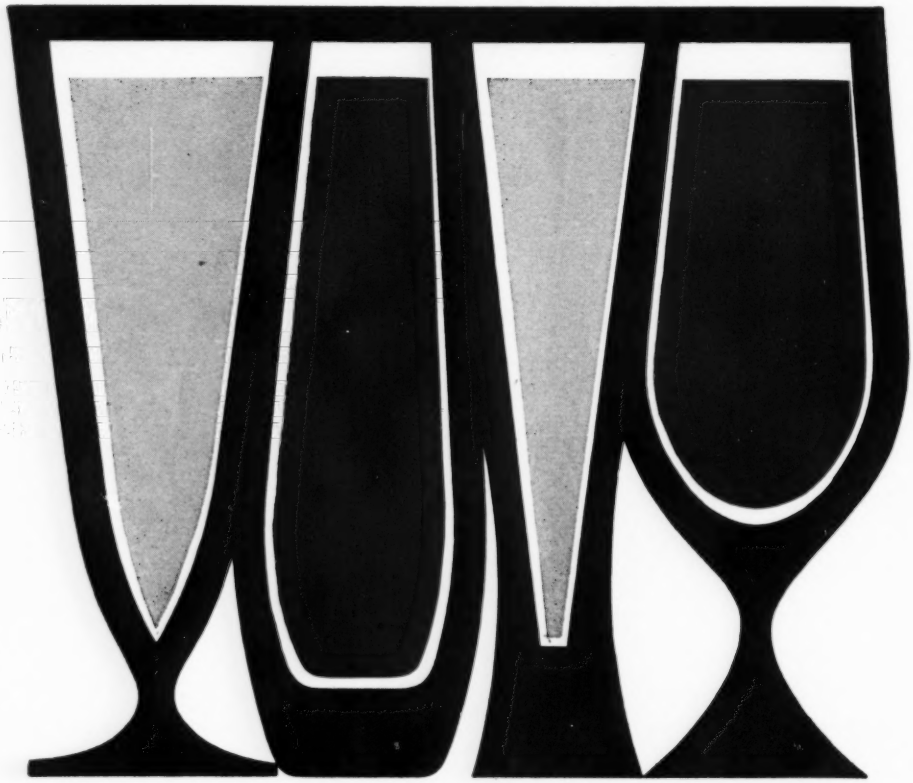
HERE'S HOW: 1. It combines a unique inner filter of ACTIVATED CHARCOAL . . . definitely proved to make the taste of a cigarette mild and smooth . . .

2. with a pure white outer filter. Together they select and balance the flavor elements in the smoke. Tareyton's **flavor-balance** gives you the best taste of the best tobaccos.

DUAL FILTER Tareyton

Product of The American Tobacco Company — "Tobacco is our middle name" © A. T. Co.

introducing a modern concept in nutrition...



Nutrament™

BRAND

nutritionally complete food

a nutritious meal, ready to drink

to supplement inadequate diets...to replace skipped meals

Nutrament provides a scientifically balanced ratio of protein-fat-carbohydrate. Each 12½-ounce serving contains: 20 grams of quality protein; 50 grams of carbohydrate; and 13.3 grams fat, with added vitamins and minerals.

...nutritional support in convenient, tasty, liquid form

- *when time, habit, or circumstance interfere with good nutrition*

  Nutrament may be used by individuals who skip breakfast or lunch or do not eat properly because of busy schedules or faulty eating habits; and by those adolescents whose poor dietary selections fail to meet their nutritional needs so important during this period of active growth.[1]

- *when nutritional deficiencies threaten or require correction*

  Nutrament also is useful for obstetric patients who often require sound, easily tolerated, and convenient nutritional supplementation during pregnancy and lactation;[2] and for geriatric and other patients who cannot or will not maintain proper nutrition because of poor dentition,[3,4] faulty eating habits,[1,3] or lack of interest in eating.[3,5]

- *when oral, dental, or surgical problems prevent ingestion of solid food*

  Nutrament liquid, sipped directly from a glass or through a straw, may be used to provide good nutrition in patients who are unable to chew solid foods or in whom solids are contraindicated.

- *when hospital and convalescent diets require supplementation*

  Even though prescribed, adequate diets may not be consumed because of the difficulty of providing personalized nutritional supplementation and encouragement of feeding.[6] Nutrament is easily adjusted to the individual patient's needs; provides excellent nutritional support; requires no special preparation.

scientifically formulated to provide all known essential nutrients

Each 12½ fl. oz. can of Nutrament liquid provides 400 calories. Caloric Distribution: protein—20%; fat—30%; carbohydrate—50%; plus following vitamins and minerals:

		%MDR
Vitamin A (U.S.P. Units)	1250	30
Vitamin D (U.S.P. Units)	125	30
Vitamin C, mg.	50	166
Thiamine, mg.	0.5	50
Riboflavin, mg.	0.6	50
Niacinamide, mg.	5.0	50
Calcium, Gm.	0.5	67
Phosphorus, Gm.	0.4	53
Iron, mg.	4	40
Iodine, mcg.	60	60
Vitamin E (Int. Units)	2.5	
Pyridoxine, mg.	0.4	
Vitamin B_{12}, mcg.	0.5	
Calcium pantothenate, mg.	2.0	
Sodium, Gm.	0.2	
Potassium, Gm.	0.9	
Copper, mg.	0.5	
Manganese, mg.	1.0	
Fiber, Gm.	0.55	

ingredients

Whole milk, skim milk, sugar, soy flour, Dextri-Maltose,® (maltose and dextrins derived from enzymic action of choice barley malt on selected corn flour) starch, chondrus extract, sodium alginate, vitamin A palmitate, calciferol, sodium ascorbate, thiamine hydrochloride, niacinamide, ferrous sulfate, sodium iodide, d-alpha-tocopheryl acetate, pyridoxine hydrochloride, cyanocobalamin, calcium pantothenate, salt, cupric carbonate, manganese sulfate, cocoa and/or vanilla flavor.

readily accepted by patients

Nutrament liquid requires no special preparation. The smooth texture and appealing taste of Nutrament make it readily acceptable. Equally delicious served hot or cold. Nutrament also has a high satiety value.

supplied

In 12½-fluid-ounce cans, chocolate and vanilla flavors. Conveniently available at drug and food stores.

references

(1) Johnston, J. A.: Ann. New York Acad. Sc. *69*:881-901 (Jan. 10) 1958. (2) Burke, B. S., and Kirkwood, S. B., in Greenhill, J. P.: Obstetrics, ed. 12, Philadelphia, W. B. Saunders Company, 1960, pp. 126-131. (3) Skillman, T. G.; Hamwi, G. J., and May, C.: Geriatrics *15*:464-472 (June) 1960. (4) Shaw, J. H., in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1960, pp. 558-601. (5) Campbell, D. G.: *ibid*, pp. 888-910. (6) Abbott, W., in Allison, J. B.: Ann. New York Acad. Sc. *69*:1018-1022 (Jan. 10) 1958.

36261

Edward Dalton Co.
A DIVISION OF
MEAD JOHNSON & COMPANY

Quality products from nutritional research

taste-tested by experts

VI-SOL®

Chewable Vitamins

TRI-VI-SOL® · POLY-VI-SOL® · DECA-VI-SOL®

In recent taste tests by over 800 children, the flavor of Vi-Sol chewable vitamins was preferred conclusively over other chewable vitamin tablets...as much as 2 to 1 in some cases.

Vi-Sol chewable vitamins now have new, improved formulations...authoritatively based* but modified to fulfill the practical needs of today's children. With these revisions, Vi-Sol chewable vitamins provide safe, rational, practical levels of C, D and A for the growing child—preschool to adolescent.

*Recommended Daily Dietary Allowances established by the National Research Council, and endorsed by the Council on Foods and Nutrition of the American Medical Association, "Vitamin Preparations As Dietary Supplements and As Therapeutic Agents," J.A.M.A. *169*:41-45 (Jan. 3) 1959.

Mead Johnson Laboratories

Symbol of service in medicine

51461